not influence the growth of human erythroid progenitors in vitro. Therefore STK-1L would not find practical application in future in vivo therapy as erythropoiesis stimulatory agent.

L2 ANSWER 3 OF 23 MEDLINE
AN 96082164 MEDLINE
DN 96082164
TI Effects of human **FLT3 ligand** on myeloid leukemia cell growth: heterogeneity in response and synergy with other hematopoietic growth factors.
AU Piacibello W; Fubini L; Sanavio F; Brizzi M F; Severino A; Garetto L; Stacchini A; Pegoraro L; Aglietta M
CS Department of Biomedical Sciences and Human Oncology, Medical School of Torino, Italy.
SO BLOOD, (1995 Dec 1) 86 (11) 4105-14.
Journal code: A8G. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199603
AB A novel hematopoietic growth factor for primitive hematopoietic progenitor cells, the ligand for the flt3/flk2 receptor, (FL), has been recently purified and its gene has been cloned. In the present study, we investigated the effects of FL on the proliferation and differentiation of normal and leukemic myeloid progenitor cells. We demonstrate that FL is a potent stimulator of the in vitro growth of granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-3 (IL-3), or G-CSF-dependent granulocyte-macrophage committed precursors from Lin- CD34+ bone marrow cells of normal donors. By contrast, FL does not affect the growth of erythroid-committed progenitors even in the presence of erythropoietin. The effect of FL on the proliferation and on the in vitro growth of clonogenic leukemic precursor cells was studied in 54 acute myeloid leukemia (AML) cases. Fresh leukemia blasts from 36 of 45 patients with AML significantly responded to FL without any relation to the French-American-British (FAB) subtype. FL stimulated the proliferation of leukemic blasts in a dose-dependent fashion. Synergistic activities were seen when FL was combined with G-CSF, GM-CSF, IL-3, or stem cell factor (SCF). FL as a single factor induced or increased significantly colony formation by clonogenic precursor cells from 21 of 24 patients with AML. In the presence of suboptimal and optimal concentrations of G-CSF, GM-CSF, IL3, SCF, or a combination of all factors, FL strongly enhanced the number of leukemic colonies (up to 18-fold). We also evaluated the induction of tyrosine phosphorylated protein on FL stimulation in fresh AML cells. We demonstrate that, on FL stimulation, a band of phosphorylated protein(s) of about 90 kD can be detected in FL-responsive, but not in FL-unresponsive cases. This study suggests that FL may be an important factor for the growth of myeloid leukemia cells, either as a direct stimulus or as a synergistic factor with other cytokines.

L2 ANSWER 4 OF 23 MEDLINE
AN 96082162 MEDLINE
DN 96082162
TI Plasma/serum levels of **flt3 ligand** are low in normal individuals and highly elevated in patients with Fanconi anemia and acquired aplastic anemia.
AU Lyman S D; Seaberg M; Hanna R; Zappone J; Brasel K; Abkowitz J L; Prchal J T; Schultz J C; Shahidi N T
CS Immunex Corporation, Seattle, WA 98101, USA.
SO BLOOD, (1995 Dec 1) 86 (11) 4091-6.
Journal code: A8G. ISSN: 0006-4971.
CY United States

DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199603
AB The **flt3 ligand** is a growth factor that stimulates the proliferation of hematopoietic progenitor and stem cells. We established a sensitive enzyme-linked immunosorbent assay (ELISA) to measure the concentration of **flt3 ligand** in plasma or serum from normal individuals, as well as in patients with hematopoietic disorders. Concentrations of **flt3 ligand** in plasma or serum from normal individuals were quite low: only 12% (7 of 60) of normal individuals had **flt3 ligand** levels above 100 pg/mL (the limit of detection). In contrast, 86% (19 of 22) of samples from patients with Fanconi anemia and 100% (eight of eight) of samples from patients with acquired aplastic anemia had plasma or serum levels above 100 pg/mL. Mean plasma or serum concentrations (calculated by assigning a value of 0 pg/mL to any sample reading below the level of detection) were as follows: normal volunteers, 14 pg/mL; patients with Fanconi anemia, 1,331 pg/mL; and patients with acquired aplastic anemia, 460 pg/mL. Concentrations of **flt3 ligand** in blood are, therefore, specifically elevated to a level that may be physiologically relevant in hematopoietic disorders with a suspected stem cell component. The elevated **flt3 ligand** concentrations in these individuals may be part of a compensatory hematopoietic response to boost the level of progenitor cells.

L2 ANSWER 5 OF 23 MEDLINE
AN 96048890 MEDLINE
DN 96048890
TI The effect of human flt-3 ligand on committed progenitor cell production from normal, aplastic anaemia and Diamond-Blackfan anaemia bone marrow.
AU Scopes J; Daly S; Ball S E; McGuckin C P; Gordon-Smith E C; Gibson F M
CS Department of Cellular and Molecular Sciences, St George's Hospital Medical School, London.
SO BRITISH JOURNAL OF HAEMATOLOGY, (1995 Nov) 91 (3) 544-50. Journal code: AXC. ISSN: 0007-1048.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199605
AB We investigated the effect of the human ligand for flt-3 (FL) on the committed progenitor colony formation of normal bone marrow (BM) (n = 9) and BM from four aplastic anaemia (AA) and three Diamond-Blackfan anaemia (DBA) patients. Methylcellulose committed progenitor cell assays were carried out using FL alone and in combinations with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-3 (IL-3) and c-kit ligand (KL). FL alone had a limited, though significant, effect on the production of granulocyte-macrophage colony-forming unit (CFU-GM) colonies from normal BM and showed an additive effect with IL-3 and GM-CSF separately, but not in combination. FL did not increase the stimulation of KL and did not have an effect on the production of erythroid progenitor colonies. FL had no effect on the AA and DBA BMs studied.

L2 ANSWER 6 OF 23 MEDLINE
AN 96032581 MEDLINE
DN 96032581
TI Structural analysis of human and murine **flt3 ligand** genomic loci.

AU Lyman S D; Stocking K; Davison B; Fletcher F; Johnson L; Escobar S
CS Immunex Research and Development Corporation, Seattle, Washington 98101, USA.
SO ONCOGENE, (1995 Sep 21) 11 (6) 1165-72.
Journal code: ONC. ISSN: 0950-9232.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-U29874; GENBANK-U29875
EM 199601
AB Both the murine and human genomic loci that encode **flt3 ligand** have been cloned. **flt3 ligand** is a hematopoietic growth factor that stimulates the proliferation of stem and progenitor cells. The portions of the murine and human **flt3 ligand** genomic loci encompassing the coding region of the protein are approximately 4.0 kb and 5.9 kb, respectively. The human genomic locus is larger as a result of the presence of repeated sequences within introns I, II, IV, V and VI. The transmembrane isoform of the murine and human **flt3 ligand** proteins are each encoded within seven exons (1-5 + 7 and 8). Analyses of **flt3 ligand** cDNA clones show that alternative splicing of a putative sixth exon results in the generation of a soluble form of the **flt3 ligand** protein. The sizes of each of the exons are well conserved between species. Murine and human flt3 genomic loci have a similar exon: intron structure compared to the genomic loci encoding Steel factor and colony stimulating factor 1. These proteins, which appear to be ancestrally related, are hematopoietic growth factors that stimulate cells via specific and structurally related tyrosine kinase receptors on the cell surface.

L2 ANSWER 7 OF 23 MEDLINE
AN 96027508 MEDLINE
DN 96027508
TI Effect of **flt3 ligand** on the ex vivo expansion of human CD34+ hematopoietic progenitor cells.
AU McKenna H J; de Vries P; Brasel K; Lyman S D; Williams D E
CS Immunex Corp, Seattle, WA 98101, USA.
SO BLOOD, (1995 Nov 1) 86 (9) 3413-20.
Journal code: A8G. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199602
AB A ligand for the tyrosine kinase receptor flt3/flk-2, referred to here as **flt3 ligand** (flt3L), was recently cloned. The effect of flt3L on purified human CD34+ progenitor cells was examined. flt3 receptor (flt3R) was detected on the surface of human bone marrow cells that were enriched for CD34 expression. The effects of flt3L and the c-kit ligand Steel factor (SLF) on hematopoietic progenitors were compared in clonal colony assays. Both factors synergized with Pixy321 (interleukin-3 [IL-3]-granulocyte-macrophage colony-stimulating factor fusion protein) to induce granulocytic-monocytic (GM) and high proliferative potential (HPP) colonies and synergized with Pixy321 + erythropoietin (EPO) to induce multipotent granulocytic-erythroid-monocytic-megakaryocytic colonies. Although SLF had a potent effect on colony formation of erythroid restricted progenitor cells (burst-forming unit-erythroid), no effect by flt3L was observed. The addition of flt3L to irradiated long-term marrow cultures seeded with CD34+ cells augmented both total and progenitor cell production. Ex vivo expansion studies with isolated CD34+ bone marrow cells from normal donors showed that flt3L alone supported

maintenance of both GM and HPP progenitors for 3 to 4 weeks in vitro. The addition of flt3L to a growth factor combination of IL-1 alpha + IL-3 + IL-6 + EPO resulted in a synergistic effect on progenitor cell expansion comparable to that observed with the addition of SLF to IL-1 alpha + IL-3 + IL-6 + EPO. These data show a function for flt3L in the regulation of both primitive multipotent and lineage-committed hematopoietic progenitor cells.

L2 ANSWER 8 OF 23 MEDLINE
AN 96019555 MEDLINE
DN 96019555
TI Biology of **flt3 ligand** and receptor.
AU Lyman S D
CS Immunex Corporation, Seattle, WA 98101, USA.
SO INTERNATIONAL JOURNAL OF HEMATOLOGY, (1995 Aug) 62 (2) 63-73. Ref: 42
Journal code: A7F. ISSN: 0925-5710.
CY Ireland
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
EM 199606
AB The **flt3 ligand** is a member of a small family of growth factors that stimulate the proliferation of hematopoietic cells; other members of this family include Steel factor (also known as mast cell growth factor, stem cell factor, and kit ligand) and colony stimulating factor 1. These proteins function by binding to and activating unique tyrosine kinase receptors. Expression of the flt3 receptor is primarily restricted among hematopoietic cells to the most primitive progenitor cells. The **flt3 ligand** is similar to Steel factor in that both proteins stimulate the proliferation of early progenitor or stem cells. Neither of these factors has much proliferative activity on its own, but each factor can synergize with a wide range of other colony stimulating factors and interleukins (ILs) to stimulate proliferation. One major difference between the two factors appears to be their effect on mast cells, which Steel factor stimulates but **flt3 ligand** does not. Although **flt3 ligand** and Steel factor each act on early hematopoietic cells, differences in their activities suggest that they are not redundant and both are required for normal hematopoiesis. There are a number of clinical settings in which the **flt3 ligand** may potentially prove quite useful.

L2 ANSWER 9 OF 23 MEDLINE
AN 95385746 MEDLINE
DN 95385746
TI **Flt3 ligand** stimulates/costimulates the growth of myeloid stem/progenitor cells.
AU Broxmeyer H E; Lu L; Cooper S; Ruggieri L; Li Z H; Lyman S D
CS Department of Medicine (Hematology/Oncology), Indiana University School of Medicine, Indianapolis 46202-5121, USA..
NC R37 CA36464 (NCI)
R01 HL46549 (NHLBI)
R01 HL49202 (NHLBI)
SO EXPERIMENTAL HEMATOLOGY, (1995 Sep) 23 (10) 1121-9.
Journal code: EPR. ISSN: 0301-472X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199512
AB The present studies evaluated effects of recombinant human (rhu) and murine (rmu) **flt3 ligand** (flt3-L) on colony

formation by subsets of myeloid stem and progenitor cells present in low-density (LD) and cell-sorted CD34 hu cord blood (CB) and bone marrow (BM) cells and unseparated mu BM cells. By itself, flt3-L had weak colony-stimulating activity. It stimulated small dispersed CFU-GM-type colonies, but not BFU-E, CFU-GEMM, or HPP-CFC colonies, from LD and CD34 huCB and BM. However, flt3-L had additive to greater-than-additive effects on colony number and size by CFU-GM stimulated with GM-CSF or IL-3, with or without Steel factor (SLF); by CFU-G stimulated by G-CSF with or without SLF; by CFU-M stimulated by CSF-1; and by BFU-E, CFU-GEMM, and HPP-CFC stimulated by Epo with or without IL-3 or SLF. Flt3-L enhanced the effects of SLF, alone and in combination with other CSFs. Similar effects were apparent on LD and sorted CD34 cells and also at the level of single sorted and isolated CD34 cells/well. Flt3-L enhanced expansion of immature subsets of huCD34(+)-column separated CB CFU-GM stimulated by the potent combination of SLF and PIXY321 (a GM-CSF/IL-3 fusion protein). While flt3-L did not enhance the replating capacity of CFU-GEMM plated in the presence of Epo and SLF, it enhanced numbers of these CFU-GEMM colonies with the capacity to be replated. Flt3-L effects were not species-specific; rhu and rmu forms were active on huCB/BM and muBM. These results demonstrate the potent direct-acting stimulating/costimulating activities of flt3-L in vitro on myeloid stem/progenitor cells.

L2 ANSWER 10 OF 23 MEDLINE
AN 95383634 MEDLINE
DN 95383634
TI Multi-level effects of **flt3 ligand** on human hematopoiesis: expansion of putative stem cells and proliferation of granulomonocytic progenitors/monocytic precursors.
AU Gabbianelli M; Pelosi E; Montesoro E; Valtieri M; Luchetti L; Samoggia P; Vitelli L; Barberi T; Testa U; Lyman S; et al
CS Department of Hematology-Oncology, Instituto Superiore di Sanit`a, Rome, Italy.
SO BLOOD, (1995 Sep 1) 86 (5) 1661-70.
Journal code: A8G. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199512
AB We have evaluated the effects of the flt3 receptor ligand (FL) on hematopoietic progenitors/stem cells (HPCs/HSCs) stringently purified from adult peripheral blood and grown in different culture systems. In these experiments HPCs/HSCs were treated with FL +/- kit ligand (KL) +/- monocyte colony-stimulatory factor (M-CSF). In clonogenetic HPC culture supplemented with interleukin-3 (IL-3)/granulomonocyte-CSF (GM-CSF)/erythropoietin (Epo), FL potentiates colony-forming unit (CFU)-GM proliferation in terms of colony number and size, but exerts little effect on burst-forming units-erythroid (BFU-E) and CFU-granulocyte erythroid megakaryocyte macrophage (CFU-GEMM) growth, whereas KL enhances the proliferation of all HPC types; combined FL+KL +/- M-CSF treatment causes a striking shift of CFU-GM colonies from granulocytic to monocytic differentiation. In liquid suspension HPC culture, FL alone induces differentiation along the monocytic and to a minor extent the basophilic lineages, whereas M-CSF alone stimulates prevalent monocytic differentiation but little cell proliferation: combined M-CSF+FL treatment causes both proliferation and almost exclusive monocytic differentiation (97% monocytes in fetal calf serum-rich (FCS+) culture conditions, mean value). At primitive HPC level, FL potentiates the clonogenetic capacity of colony-forming units-blast (CFU-B) and high proliferative potential colony-forming cells (HPP-CFC) in primary and secondary culture; KL exerts a similar action, and additive effects are induced by FL combined with KL.

More important, addition of FL alone causes a significant amplification of the number of long-term culture-initiating cells (LTC-ICs), ie, putative repopulating HSCs, whereas this effect is not induced by KL. The FL effects correlate with flt3 mRNA expression in HPCs differentiating throught the erythroid or GM pathway in liquid suspension culture: (1) flt3 mRNA is expressed in freshly purified, resting HPCs; after growth factor stimulus the message (2) is abruptly down-modulated in HPC erythroid differentiation, but (3) is sustainedly expressed through HPC GM differentiation and abolished in GM precursor maturation. This pattern contrasts with the gradual downmodulation of c-kit through both erythroid and GM HPC differentiation. The results indicate that FL exerts a stimulatory action on primitive HPCs, including a unique expanding effect on putative stem cells, whereas its distal proliferative/differentiative action is largely restricted to CFU-GM and monocytic precursors. The latter effect is potentiated by KL and M-CSF, thus suggesting that the structural similarities of FL, KL, M-CSF, and their tyrosine kinase receptors may mediate positive interactions of these growth factors son monocytic differentiation.

L2 ANSWER 11 OF 23 MEDLINE
AN 95371366 MEDLINE
DN 95371366
TI Expression of FLT3 receptor and **FLT3-ligand** in human leukemia-lymphoma cell lines.
AU Meierhoff G; Dehmel U; Gruss H J; Rosnet O; Birnbaum D; Quentmeier H; Dirks W; Drexler H G
CS German Collection of Microorganisms and Cell Cultures, Braunschweig.
SO LEUKEMIA, (1995 Aug) 9 (8) 1368-72.
Journal code: LEU. ISSN: 0887-6924.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199511
AB The FLT3 gene encodes a receptor tyrosine kinase that is closely related to two well-known receptors, KIT and FMS, that regulate with their respective ligands, stem cell factor (SCF) and macrophage colony-stimulating factor (M-CSF), proliferation and differentiation of hematopoietic cells. The ligand for FLT3, FL, is active in both soluble and membrane-bound forms. We examined expression of FL and FLT3 mRNA in a panel of some 110 continuous human leukemia-lymphoma cell lines from all major hematopoietic cell lineages by Northern blot analysis. FLT3 mRNA is expressed primarily in pre-B cell lines, myeloid and monocytic cell lines whereas FL mRNA was detected in most cell lines from all cell lineages. Analysis of FLT3 receptor protein expression examined with a specific anti-FLT3 monoclonal antibody and flow cytometry in 17 cell lines confirmed the results obtained at the mRNA level. Forty of 110 cell lines displayed both receptor and ligand mRNA suggesting a possible autocrine or intracrine stimulation. In normal hematopoietic cells expression of FLT3 was reported to be associated with CD34 positivity, a cell surface marker of immature and precursor cells. No correlation between FLT3 and CD34 expression was found in the cell lines analyzed. These studies served to illustrate further the importance of the FL-**FLT3 ligand**-receptor system in the regulation of hematopoietic cells.

L2 ANSWER 12 OF 23 MEDLINE
AN 95356573 MEDLINE
DN 95356573
TI Expression of the flt3 receptor and its ligand on hematopoietic cells.
AU Brasel K; Escobar S; Anderberg R; de Vries P; Gruss H J; Lyman S D
CS Department of Immunobiology, Immunex Research and Development

Corporation, Seattle, Washington 98101, USA.
SO LEUKEMIA, (1995 Jul) 9 (7) 1212-8.
Journal code: LEU. ISSN: 0887-6924.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199511
AB Expression of the flt3 tyrosine kinase receptor and its ligand were examined on various murine and human hematopoietic cell lines. Surface expression of flt3 receptor and **flt3 ligand** were detected by flow cytometry using biotinylated human **flt3 ligand** or biotinylated soluble human flt3 receptor Fc fusion protein (flt3R-Fc), respectively. Flt3 receptor and ligand expression were also examined by Northern blot analysis. Flt3 receptor was expressed on the surface of only two of nine murine cell lines and nine of 15 human cell lines, with positive cells representing the B cell, early myeloid, and monocytic lineages. Staining for surface expression of the **flt3 ligand** revealed that seven of nine murine cell lines and nine of 15 human cell lines screened were positive by flow cytometry. All murine and human cell lines assayed were positive for **flt3 ligand** RNA expression by Northern blot analysis, but not all cell lines expressing **flt3 ligand** mRNA had detectable surface expression. Cells expressing the **flt3 ligand** were of the myeloid, B cell and T cell lineages at various stages of differentiation. Only the OCI-AML-5, NALM-6, and AML-193 cell lines coexpressed both surface flt3 receptor and ligand. The myeloid leukemic M1 cell terminally differentiate into macrophage-like cells under the influence of leukemia inhibitory factor (LIF). We found that LIF-stimulated M1 cells down-regulated surface expression and mRNA levels of the flt3 receptor, but up-regulated expression of the **flt3 ligand**. Although we could demonstrate that the flt3 receptor was functional in the M1 cell line, **flt3 ligand** could not induce the M1 cells to differentiate.

L2 ANSWER 13 OF 23 MEDLINE
AN 95268062 MEDLINE
DN 95268062
TI Commentary: a rapid proliferation assay for unknown co-stimulating factors in cord blood plasma possibly involved in enhancement of in vitro expansion and replating capacity of human hematopoietic stem/progenitor cells [comment].
CM Comment on: Blood Cells 1994;20(2-3):482-90; discussion 491
AU Broxmeyer H E; Benninger L; Yip-Schneider M; Braun S E
CS Department of Medicine (Hematology/Oncology), Indiana University, Indianapolis, USA..
NC R37 CA36464 (NCI)
R01 HL46549 (NHLBI)
R01 HL49202 (NHLBI)
+
SO BLOOD CELLS, (1994) 20 (2-3) 492-7.
Journal code: A8H. ISSN: 0340-4684.
CY United States
DT Commentary
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199508

L2 ANSWER 14 OF 23 MEDLINE
AN 95261038 MEDLINE
DN 95261038
TI FLT3/FLK2 ligand promotes the growth of murine stem cells and the

expansion of colony-forming cells and spleen colony-forming units.
AU Hudak S; Hunte B; Culpepper J; Menon S; Hannum C; Thompson-Snipes L; Rennick D
CS Department of Immunology, DNAX Research Institute of Molecular and Cellular Biology, Palo Alto, CA 94304, USA..
SO BLOOD, (1995 May 15) 85 (10) 2747-55.
Journal code: A8G. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199508
AB The effect of FLT3/FLK2 ligand (FL) on the growth of primitive hematopoietic cells was investigated using ThyloSca1+ stem cells. FL was observed to interact with a variety of factors to initiate colony formation by stem cells. When stem cells were stimulated in liquid culture with FL plus interleukin (IL)-3, IL-6, granulocyte colony-stimulating factor (G-CSF), or stem cell factor (SCF), cells capable of forming colonies in secondary methylcellulose cultures (CFU-c) were produced in high numbers. However, only FL plus IL-6 supported an increase in the number of cells capable of forming colonies in the spleens of irradiated mice (CFU-s). Experiments with accessory cell-depleted bone marrow (Lin- BM) showed that FL alone lacks significant colony-stimulating activity for progenitor cells. Nevertheless, FL enhanced the growth of granulocyte-macrophage progenitors (CFU-GM) in cultures containing SCF, G-CSF, IL-6, or IL-11. In these assays, FL increased the number of CFU-GM initiating colony formation (recruitment), as well as the number of cells per colony (synergy). Many of the colonies were macroscopic and contained greater than 2 x 10(4) granulocytes and macrophages. Therefore, FL appears to function as a potent costimulus for primitive cells of high proliferative potential (HPP). FL was also observed to costimulate the expansion of CFU-GM in liquid cultures of Lin- BM. In contrast, FL had no growth-promoting affects on progenitors committed to the erythrocyte, megakaryocyte, eosinophil, or mast cell lineages.

L2 ANSWER 15 OF 23 MEDLINE
AN 95218174 MEDLINE
DN 95218174
TI The **flt3 ligand** supports proliferation of lymphohematopoietic progenitors and early B-lymphoid progenitors.
AU Hirayama F; Lyman S D; Clark S C; Ogawa M
CS Department of Medicine, Medical University of South Carolina, Charleston, USA..
NC DK 32294 (NIDDK)
SO BLOOD, (1995 Apr 1) 85 (7) 1762-8.
Journal code: A8G. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199507
AB We have examined the effects of the murine ligand (FL) for the flt3/flk2 tyrosine kinase receptor on the proliferation of murine lymphohematopoietic progenitors as well as committed myeloid and B-cell progenitors. In the presence of erythropoietin, FL alone supported scant colony formation from enriched marrow cells of normal mice. However, when it was combined with interleukin-3 (IL-3), steel factor (SF), or IL-11, FL significantly enhanced colony formation. When tested on enriched marrow cells from 5-fluorouracil (5-FU)-treated mice, FL neither enhanced IL-3-dependent colony formation nor synergized with SF in support of colony formation. However, FL synergized with IL-6, IL-11, or granulocyte-colony stimulating factor (G-CSF) in support of

formation of various types of colonies, including multilineage colonies. Approximately 30% of these colonies yielded pre-B-cell colonies when replated in secondary cultures containing SF and IL-7, indicating that 2-cytokine combinations, including FL and IL-6, IL-11, or G-CSF can support the proliferation of primitive lymphohematopoietic progenitors. FL, by itself and in synergy with IL-7 or SF, supported the proliferation of B-cell progenitors. These results show that FL has a wide range of activities in early hematopoiesis and B lymphopoiesis.

L2 ANSWER 16 OF 23 MEDLINE
AN 95213660 MEDLINE
DN 95213660
TI The **FLT3 ligand** potently and directly stimulates the growth and expansion of primitive murine bone marrow progenitor cells in vitro: synergistic interactions with interleukin (IL) 11, IL-12, and other hematopoietic growth factors.
AU Jacobsen S E; Okkenhaug C; Myklebust J; Veiby O P; Lyman S D
CS Department of Immunology, Norwegian Radium Hospital, Oslo..
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1995 Apr 1) 181 (4) 1357-63. Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199507
AB The recently cloned murine **flt3 ligand** (FL) was studied for its ability to stimulate the growth of primitive (Lin-Sca-1+) and more committed (Lin-Sca-1-) murine bone marrow progenitor cells, alone and in combination with other hematopoietic growth factors (HGFs). Whereas FL was a weak proliferative stimulator alone, it potently synergized with a number of other HGFs, including all four colony-stimulating factor (CSF), interleukin (IL) 6, IL-11, IL-12, and stem cell factor (SCF), to promote the colony formation of Lin-Sca-1+, but not Lin-Sca-1- or erythroid progenitor cells. The synergistic activity of FL was concentration dependent, with maximum stimulation occurring at 250 ng/ml, and was observed when cells were plated at a concentration of one cell per culture, suggesting that its effects are directly mediated. 2 wk of treatment with FL in combination with IL-3 or SCF resulted in the production of a high proportion of mature myeloid cells (granulocytes and macrophages), whereas the combination of FL with G-CSF, IL-11, or IL-12 resulted predominantly in the formation of cells with an immature blast cell appearance. Accordingly, FL in combination with G-CSF or IL-11 expanded the number of progenitors more than 40-fold after 2 wk incubation. Thus, FL emerges as a potent synergistic HGF, that in combination with numerous other HGFs, can directly stimulate the proliferation, myeloid differentiation, and expansion of primitive hematopoietic progenitor cells.

L2 ANSWER 17 OF 23 MEDLINE
AN 95211033 MEDLINE
DN 95211033
TI The **flt3 ligand**: a hematopoietic stem cell factor whose activities are distinct from steel factor.
AU Lyman S D; Brasel K; Rousseau A M; Williams D E
CS Immunex Research and Development Corporation, Seattle, Washington.
SO STEM CELLS, (1994) 12 Suppl 1 99-107; discussion 108-10. Ref: 28 Journal code: BN2. ISSN: 1066-5099.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English

FS Priority Journals
EM 199507
AB A number of growth factors have been described that affect the hematopoietic system. Among this group are Steel factor (also known as mast cell growth factor, stem cell factor and kit ligand), and the more recently described **flt3 ligand**. These factors have been shown to function by binding to and activating the c-kit and flt3 tyrosine kinase receptors, respectively. Both of these factors stimulate the growth of mouse and human hematopoietic progenitor cells. These factors therefore differ from such later acting hematopoietic factors as colony-stimulating factor (CSF)-1, which regulates the growth, survival and differentiation of monocytic cells through the c-fms tyrosine kinase receptor. Like Steel factor, the **flt3 ligand** has little biological activity on its own, but synergizes well with a number of other colony stimulating factors and interleukins. One major difference between the two factors appears to be their effect on mast cells. Steel factor stimulates both the proliferation and activation of mast cells, while preliminary data with the **flt3 ligand** suggests that it has no effect on mast cells. Although the **flt3 ligand** and Steel factor each act on early hematopoietic cells, differences in their activities suggest that they are not redundant and are both required for normal hematopoiesis.

L2 ANSWER 18 OF 23 MEDLINE
AN 95211012 MEDLINE
DN 95211012
TI TNF-alpha, the great imitator: role of p55 and p75 TNF receptors in hematopoiesis.
AU Jacobsen S E; Jacobsen F W; Fahlman C; Rusten L S
CS Department of Immunology, Norwegian Radium Hospital, Oslo.
SO STEM CELLS, (1994) 12 Suppl 1 111-26; discussion 126-8. Ref: 105
Journal code: BN2. ISSN: 1066-5099.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199507
AB The clinical application of tumor necrosis factor-alpha (TNF-alpha) has so far been limited due to the severe adverse effects associated with its systemic use. Recently, two distinct TNF receptors with molecular weights of 55 kDa (TNFR55) and 75 kDa (TNFR75) have been cloned and characterized. The subsequent development of TNF-alpha mutants with selective activity on either TNFR55 or TNFR75 suggest that such mutants might maintain the therapeutic (anti-tumor) potential of wild type TNF-alpha, but exhibit reduced toxicity (proinflammatory effects). In the present article we discuss previous studies on the effects of TNF-alpha in in vitro and in vivo hematopoiesis. In addition, we summarize more recent data from our laboratory as well as others, elucidating the role of TNF-alpha as a direct bifunctional regulator of in vitro hematopoiesis. Specifically, TNF-alpha is a potent inhibitor of the clonal growth of primitive and committed murine and human bone marrow progenitors in combination with multiple cytokines, including granulocyte colony-stimulating factor (G-CSF), CSF-1, erythropoietin (Epo), stem cell factor (SCF), and **flt3 ligand** (FL). In contrast, TNF-alpha at low concentrations can synergistically and directly enhance the clonal growth of primitive and more mature human CD34+ bone marrow progenitors when combined with GM-CSF or interleukin (IL)-3. Thus, a critical determinant of whether TNF-alpha elicits a stimulatory or inhibitory effect on the in vitro growth of hematopoietic progenitors appears to be the specific

growth factors with which it interacts, rather than the maturity of the targeted progenitor. Furthermore, we describe the involvement of the two TNF receptors in signaling in vitro hematopoietic effects of TNF-alpha. Whereas TNFR55 is involved in most observed responses to TNF-alpha, signaling of TNFR75 appears to be restricted to inhibitory effects on primitive progenitors. Finally, we discuss the complexity of direct and indirect actions of TNF-alpha in in vivo hematopoiesis, and the potential clinical applications of TNF-alpha or TNF mutants.

L2 ANSWER 19 OF 23 MEDLINE
AN 95124710 MEDLINE
DN 95124710
TI Identification of soluble and membrane-bound isoforms of the murine **flt3 ligand** generated by alternative splicing of mRNAs.
AU Lyman S D; James L; Escobar S; Downey H; de Vries P; Brasel K; Stocking K; Beckmann M P; Copeland N G; Cleveland L S; et al
CS Immunex Research and Development Corporation, Seattle, Washington 98101.
NC N01-CO-74101 (NCI)
SO ONCOGENE, (1995 Jan 5) 10 (1) 149-57.
Journal code: ONC. ISSN: 0950-9232.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-S76459; GENBANK-S76461; GENBANK-S76464
EM 199504
AB We have recently described a novel hematopoietic growth factor, referred to as the **flt3 ligand**, that stimulates the proliferation of sub-populations of hematopoietic cells that are enriched for stem and progenitor cells. This factor is a transmembrane protein that undergoes proteolytic cleavage to generate a soluble form of the protein. We have isolated additional **flt3 ligand** isoforms by PCR that contain an extra exon and encode what are predicted to be either a soluble form of the ligand or a longer version of the transmembrane protein. We have also isolated cDNAs from murine T cell libraries that encode an isoform of the **flt3 ligand** that has an unusual C-terminus. This isoform results from a failure to splice out an intron during mRNA processing. The protein encoded by this cDNA is expressed on the cell surface, where it is biologically active. However, this novel isoform does not appear to give rise to a soluble form of the protein. Regulation of mRNA splicing is likely to control the generation of cell bound or soluble forms of this hematopoietic growth factor. Genetic mapping studies localize the gene encoding the **flt3 ligand** to the proximal portion of mouse chromosome 7 and to human chromosome 19q13.3.

L2 ANSWER 20 OF 23 MEDLINE
AN 95003966 MEDLINE
DN 95003966
TI Analysis of the mitogenic pathway of the FLT3 receptor and characterization in its C terminal region of a specific binding site for the PI3' kinase.
AU Casteran N; Rottapel R; Beslu N; Lecocq E; Birnbaum D; Dubreuil P
CS Molecular and Functional Hematology Laboratory, Unite 119, INSERM, Marseille, France.
SO CELLULAR AND MOLECULAR BIOLOGY, (1994 May) 40 (3) 443-56.
Journal code: BNA.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

EM 199501
AB The FLT3 receptor tyrosine kinase (RTK) belongs to the class III subfamily which includes PDGF, CSF1 and SLF receptors. The recent cloning of the **FLT3 ligand** suggesting its important role in the differentiation and proliferation of the hematopoietic stem cells, has confirmed the initial expression analysis showing restricted pattern of receptor expression within the primitive hematopoietic population. To better understand the function of the FLT3 receptor and its relationship with the other hematopoietic RTKs, we analyzed the mitogenic pathway and substrate specificity of this receptor. The construction of a chimeric receptor called FF3, between the extracellular region of the CSF1 receptor fused with the transmembrane and the cytoplasmic regions of FLT3, has allowed an analysis in the absence of **FLT3 ligand**. We have shown in previous studies that FF3 is able to transduce the signal induced by CSF1, to induce tyrosine phosphorylation and/or association of several cytoplasmic proteins. We show here that this new receptor is fully functional in Ba/F3 hematopoietic cells, inducing a CSF1 dependence when expressed at the surface of this IL3 dependent cell line. The PI3' Kinase interacts with the FF3 receptor through SH2 domains and its binding site is localized on the tyrosine residue 958 in the C terminal part of the receptor.

L2 ANSWER 21 OF 23 MEDLINE
AN 94235842 MEDLINE
DN 94235842
TI Cloning of the human homologue of the murine **flt3 ligand**: a growth factor for early hematopoietic progenitor cells.
AU Lyman S D; James L; Johnson L; Brasel K; de Vries P; Escobar S S; Downey H; Splett R R; Beckmann M P; McKenna H J
CS Department of Molecular Genetics, Immunex Research and Development Corp, Seattle, WA 98101..
SO BLOOD, (1994 May 15) 83 (10) 2795-801.
Journal code: A8G. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
OS GENBANK-U03858
EM 199408
AB Using a fragment of the murine **flt3 ligand** as a probe, we have succeeded in cloning a human **flt3 ligand** from a human T-cell lambda gt10 cDNA library. The human and murine ligands are 72% identical at the amino acid level. Analysis of multiple cDNA clones shows that alternative splicing of the human flt3 mRNA can occur at a number of positions. A recombinant soluble form of the human **flt3 ligand** stimulates the proliferation and colony formation of a subpopulation of human bone marrow cells that are CD34+ and are enriched for primitive hematopoietic cells. In addition, the human **flt3 ligand** also stimulates the proliferation of cells expressing murine flt3 receptors. Northern blot analysis shows widespread expression of **flt3 ligand** mRNA transcripts in human tissues.

L2 ANSWER 22 OF 23 MEDLINE
AN 94195428 MEDLINE
DN 94195428
TI Ligand for FLT3/FLK2 receptor tyrosine kinase regulates growth of haematopoietic stem cells and is encoded by variant RNAs.
AU Hannum C; Culpepper J; Campbell D; McClanahan T; Zurawski S; Bazan J F; Kastelein R; Hudak S; Wagner J; Mattson J; et al
CS DNAX Research Institute of Molecular and Cellular Biology, Palo

Alto, California 94304-1104..
SO NATURE, (1994 Apr 14) 368 (6472) 643-8.
Journal code: NSC. ISSN: 0028-0836.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-U04806; GENBANK-U04807
EM 199407
AB The FLT3/FLK2 receptor tyrosine kinase is closely related to two receptors, c-Kit and c-Fms, which function with their respective ligands, Kit ligand and macrophage colony-stimulating factor to control differentiation of haematopoietic and non-haematopoietic cells. FLT3/FLK2 is thought to be present on haematopoietic stem cells and found in brain, placenta and testis. We have purified to homogeneity and partially sequenced a soluble form of the FLT3/FLK2 ligand produced by mouse thymic stromal cells. We isolated several mouse and human complementary DNAs that encode polypeptides with identical N termini and different C termini. Some variants contain hydrophobic transmembrane segments, suggesting that processing may be required to release soluble ligand. The purified ligand enhances the response of mouse stem cells and a primitive human progenitor cell population to other growth factors such as interleukins IL-3 and IL-6 and to granulocyte-macrophage colony-stimulating factor, and also stimulates fetal thymocytes.

L2 ANSWER 23 OF 23 MEDLINE
AN 94084791 MEDLINE
DN 94084791
TI Molecular cloning of a ligand for the flt3/flk-2 tyrosine kinase receptor: a proliferative factor for primitive hematopoietic cells.
AU Lyman S D; James L; Vanden Bos T; de Vries P; Brasel K; Gliniak B; Hollingsworth L T; Picha K S; McKenna H J; Splett R R; et al
CS Immunex Research and Development Corporation, Seattle, Washington 98101..
SO CELL, (1993 Dec 17) 75 (6) 1157-67.
Journal code: CQ4. ISSN: 0092-8674.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-L23636; GENBANK-L20821; GENBANK-L20822; GENBANK-L20823; GENBANK-L20888; GENBANK-L20889; GENBANK-S60904; GENBANK-S60905; GENBANK-S60924; GENBANK-L33709
EM 199403
AB Cloning of a ligand for the murine flt3/flk-2 tyrosine kinase receptor was undertaken using a soluble form of the receptor to identify a source of ligand. A murine T cell line, P7B-0.3A4, was identified that appeared to express a cell surface ligand for this receptor. A cDNA clone was isolated from an expression library prepared from these cells that was capable, when transfected into cells, of conferring binding to a soluble form of the flt3/flk-2 receptor. The cDNA for this ligand encodes a type I transmembrane protein that stimulates the proliferation of cells transfected with the flt3/flk-2 receptor. A soluble form of the ligand stimulates the proliferation of defined subpopulations of murine bone marrow and fetal liver cells as well as human bone marrow cells that are highly enriched for hematopoietic stem cells and primitive uncommitted progenitor cells.

=> s (l1 or fl) and dendritic

2365 FL
15784 DENDRITIC
L3 38 (L1 OR FL) AND DENDRITIC

=> s l2 and l3

L4 0 L2 AND L3

=> d l3 1-20 bib ab

L3 ANSWER 1 OF 38 MEDLINE
AN 1998071089 MEDLINE
DN 98071089
TI Lymphoid cell aggregates: a useful clue in the fine-needle aspiration diagnosis of follicular lymphomas.
AU Suh Y K; Shabaik A; Meurer W T; Shin S S
CS Department of Pathology, University of California San Diego Medical Center, San Diego 92103-8720, USA.
SO DIAGNOSTIC CYTOPATHOLOGY, (1997 Dec) 17 (6) 467-71.
Journal code: EAH. ISSN: 8755-1039.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199803
EW 19980304
AB Among the various types of lymphoma, follicular lymphoma (**FL**) is known to have significant limitations in cytologic diagnosis by the fine-needle aspiration (FNA) method. The diagnostic accuracy (DA) for non-Hodgkin's lymphoma (NHL) by FNA was evaluated by review of 82 cases of histologically proved NHL after prior FNA. The DA for all NHLs was 66% (54/82), and that for low-grade lymphomas, including small lymphocytic lymphoma, follicular small-cleaved cell lymphoma, and follicular mixed cell lymphoma, was 71% (12/17). The DA for **FL** was 69% (11/16). Review of individual surgical and cytologic materials from FLs revealed a tendency to show fibrosis in the cytologically false-negative group and diffuse areas of lymphoma in the true-positive group. The presence of "aggregation" of uniform lymphoid cells, probably due to cell adhesions with the support of **dendritic** reticulum cells, was seen in 55% of true-positive **FL** (6/11). In contrast, only 28% of true-positive diffuse large cell lymphomas (5/18) showed a mild degree of aggregation, and none of 7 cases of true-positive diffuse small-cleaved cell lymphoma showed this feature. The aggregation of cells was not pathognomonic of **FL**, but its presence with a homogeneous cellular constituent and the paucity of tingible-body macrophages helped us to predict **FL**. Also, it was a feature distinguishing **FL** from diffuse small-cleaved cell lymphoma (P = 0.025).

L3 ANSWER 2 OF 38 MEDLINE
AN 1998026144 MEDLINE
DN 98026144
TI In vivo administration of **flt3 ligand** markedly stimulates generation of **dendritic** cell progenitors from mouse liver.
AU Drakes M L; Lu L; Subbotin V M; Thomson A W
CS Thomas E. Starzl Transplantation Institute, University of Pittsburgh, PA 15213, USA.
NC DK49745 (NIDDK)
AI41011 (NIAID)
SO JOURNAL OF IMMUNOLOGY, (1997 Nov 1) 159 (9) 4268-78.
Journal code: IFB. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 199801
EW 19980104
AB The study of liver **dendritic** cells (DC) and their progenitors is restricted by the small numbers that can be isolated or propagated from normal hepatic tissue. We examined the ex vivo growth, phenotype, and function of these cells after the administration to mice of the recently cloned hemopoietic growth factor **flt3 ligand** (**FL**), which is highly effective in mobilizing stem/progenitor cells. **FL** treatment (10 microg/day for 10 days) resulted in a mean 14-fold increase in the absolute number of nonparenchymal cells recovered from collagenase-digested livers compared with the control value. Culture of these nonparenchymal cells in granulocyte-macrophage CSF (GM-CSF; 1000 U/ml) resulted in the early formation of proliferating cell clusters and maximal release (within 4-5 days) of markedly increased numbers of nonadherent, low buoyant density cells per liver. Maximal release of low buoyant density cells propagated from control livers was at the later time of 6 to 8 days. Cells from both sources were DEC-205+, CD11c+, MHC class II+, CD80(low) (i.e., low level of CD80), CD86(low) and CD40(low). This immature phenotype was linked to poor T cell allostimulatory activity, indicative of DC progenitors. Propagation of cells from livers of **FL** -treated mice in GM-CSF and IL-4 resulted in a more mature DC phenotype and function. Maturational changes were also observed following exposure of the GM-CSF-stimulated progenitors to type 1 collagen for 3 additional days. The ability of **FL** to boost production of large numbers of liver DC progenitors provides opportunities for the further study of these important APC in normal liver immunobiology and in immune-mediated hepatic disorders.

L3 ANSWER 3 OF 38 MEDLINE
AN 97471004 MEDLINE
DN 97471004
TI Murine hematopoietic stem cells committed to macrophage/ **dendritic** cell formation: stimulation by Flk2-ligand with enhancement by regulators using the gp130 receptor chain.
AU Metcalf D
CS The Walter and Eliza Hall Institute of Medical Research, Post Office Royal Melbourne Hospital, 3050 Victoria, Australia.
NC CA22556 (NCI)
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Oct 14) 94 (21) 11552-6.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199801
EW 19980104
AB The stimulation by Flk2-ligand (**FL**) of blast colony formation by murine bone marrow cells was selectively potentiated by the addition of regulators sharing in common the gp130 signaling receptor-leukemia inhibitory factor (LIF), oncostatin M, interleukin 11, or interleukin 6. Recloning of blast colony cells indicated that the majority were progenitor cells committed exclusively to macrophage formation and responding selectively to proliferative stimulation by macrophage colony-stimulating factor. Reculture of blast colony cells initiated by **FL** plus LIF in cultures containing granulocyte/macrophage colony-stimulating factor plus tumor necrosis factor alpha indicated that at least some of the cells were capable of maturation to **dendritic** cells. The cells forming blast colonies in response to **FL** plus LIF were unrelated to those forming blast colonies in response to stimulation by stem cell factor and appear to be a distinct subset of mature hematopoietic stem cells.

L3 ANSWER 4 OF 38 MEDLINE
AN 97465478 MEDLINE
DN 97465478
TI **Dendritic** cells generated from the blood of patients with multiple myeloma are phenotypically and functionally identical to those similarly produced from healthy donors.
AU Pfeiffer S; Gooding R P; Apperley J F; Goldschmidt H; Samson D
CS Department of Haematology, Royal Postgraduate Medical School, Hammersmith Hospital, London, U.K.
SO BRITISH JOURNAL OF HAEMATOLOGY, (1997 Sep) 98 (4) 973-82. Journal code: AXC. ISSN: 0007-1048.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199802
EW 19980204
AB Using a combination of GM-CSF, SCF, flk-2/flt-3 ligand, and IL-4, **dendritic** cells (DC) have been generated in vitro from the adherent fraction of mononuclear cells isolated from the blood of patients with MM. Analysis of cell yield showed no significant difference in DC yield (numbers or percentage of leucocytes) or total number of leucocytes generated in myeloma cultures compared to similar cultures prepared using mononuclear cells from the blood of healthy donors. The mean number of DC produced after 10d of culture were 8.19 x 10(5) and 9.87 x 10(5) cells (41% and 51% of all leucocytes) for the myeloma and normal cultures respectively. Flow cytometry investigation of phenotypic markers including CD1a, HLA-DR, CD80 (BB1/B7.1) and CD86 (B70/B7.2), and functional status (stimulatory potential in allogeneic mixed leucocyte reactions (MLR)) confirmed the generation of cells phenotypically identified as cultured DC. In addition, these cells were more effective than PBMC at stimulating allogeneic PBMC proliferation. These data demonstrate no difference between DC generated from patients with MM and healthy donors. This study was considered a prerequisite for future investigations directed towards developing effective immunotherapies for myeloma.

L3 ANSWER 5 OF 38 MEDLINE
AN 97462640 MEDLINE
DN 97462640
TI Efficient retrovirus-mediated gene transfer of **dendritic** cells generated from CD34+ cord blood cells under serum-free conditions.
AU Bello-Fernandez C; Matyash M; Strobl H; Pickl W F; Majdic O; Lyman S D; Knapp W
CS Vienna International Research Cooperation Center at Novartis Forschungsinstitut, University of Vienna, Austria.
SO HUMAN GENE THERAPY, (1997 Sep 20) 8 (14) 1651-8. Journal code: A12. ISSN: 1043-0342.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
EW 19980104
AB A retroviral-vector encoding the low affinity nerve growth factor receptor (LNGFR) was used to transduce **dendritic** cells (DCs) generated from CD34+ cord blood (CB) progenitor cells under serum-free conditions. Transduction efficiency was monitored by flow cytometry (FACS) using a specific monoclonal antibody. Prior to retroviral infections, CD34+ CB cells were stimulated for 60 h in a serum-free medium containing a DC differentiation inducing cytokine cocktail: stem cell factor (SCF), granulocyte/macrophage-colony

stimulating factor (GM-CSF), tumor necrosis factor alpha (TNFalpha), and transforming growth factor beta 1 (TGF-beta1). Addition of **flt3-ligand** (**FL**) to the aforementioned growth factors significantly enhanced cell expansion (41.7+/-11.5 fold vs. 22.5+/-4.7 fold without **FL**) and generation of CD1a+ DCs (mean 45.7+/-9.8% vs. 28+/-6.5% without **FL**, n = 4,p = 0.01). Furthermore, **FL** significantly increased the proportion of CD1a+LNGFR+ cells (mean 10%+/-4.4% vs. 6%+/-2.4 without **FL** n = 4, p = 0.03). When serum-free viral supernatants were used to infect DCs progenitors under entirely serum-free conditions and with the most potent cytokine combination, approximately one-third of the CD1a+ DCs generated co-expressed the LNGFR gene. Moreover, the transduced gene was also identified in more mature CD1a+CD80+ and CD1a+CD86+ DCs after 12-14 days of culture. In addition, transduced CD1a+ DCs maintained their functional properties, stimulating allogeneic T cells with similar efficiency as nontransduced CD1a+ DCs. Thus, the serum-free system described allows efficient generation and transduction of CD1a+ DCs derived from CD34+ progenitor cells and may be very useful for future therapeutic applications of DCs.

L3 ANSWER 6 OF 38 MEDLINE
AN 97441118 MEDLINE
DN 97441118
TI Ethanol consumption following recovery from unilateral damage to the forelimb area of the sensorimotor cortex: reinstatement of deficits and prevention of **dendritic** pruning.
AU Kozlowski D A; Hilliard S; Schallert T
CS Department of Psychology and Institute for Neuroscience, University of Texas at Austin, 78712, USA.. kozlowsk@neurosurg.medsch.ucla.edu
NC NS23964 (NINDS)
AA 07471 (NIAAA)
SO BRAIN RESEARCH, (1997 Jul 25) 763 (2) 159-66.
Journal code: B5L. ISSN: 0006-8993.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199712
EW 19971204
AB Unilateral injury to the forelimb-representation area of the sensorimotor cortex (**FL**-SMC) in adult rats results in use-dependent proliferation of **dendritic** processes, followed by partial pruning, of layer V pyramidal neurons of the contralateral homotopic cortex. In development, 'exuberant' growth of neurons is often followed by pruning, a process that has been associated with a glutamatergic-NMDA receptor mechanism. A related mechanism may play a role in injury-related pruning of dendrites in adults. The N-methyl-D-aspartate (NMDA) receptor antagonist MK801, administered throughout the pruning phase to adult animals with **FL**-SMC lesions, prevents **dendritic** pruning and disrupts behavioral recovery. Ethanol (ETOH) also acts as an NMDA receptor antagonist. It has been shown to reduce NMDA-active ion currents, inhibit NMDA-evoked electrophysiological responses, and decrease glutamate-binding in the hippocampus and cortex. ETOH also affects neuromorphology in the developing and adult cerebellum, hippocampus, and cortex. Ethanol's involvement with NMDA receptor function and its influence on **dendritic** morphology led us to examine its effect on **dendritic** pruning and behavioral recovery following unilateral **FL**-SMC lesions. Lesioned animals were exposed to moderate doses of ethanol in a liquid diet only during the period of **dendritic** pruning. As with MK801, ETOH prevented pruning and reinstated chronic behavioral asymmetries.

L3 ANSWER 7 OF 38 MEDLINE
AN 97438139 MEDLINE
DN 97438139
TI New molecule under study: **Flt3 ligand** may mobilize **dendritic** cells [news].
AU McBride G
SO JOURNAL OF THE NATIONAL CANCER INSTITUTE, (1997 Sep 3) 89 (17) 1257.
Journal code: J9J. ISSN: 0027-8874.
CY United States
DT News Announcement
LA English
FS Priority Journals; Cancer Journals
EM 199711
EW 19971104

L3 ANSWER 8 OF 38 MEDLINE
AN 97432461 MEDLINE
DN 97432461
TI The influence of collagen, fibronectin, and laminin on the maturation of **dendritic** cell progenitors propagated from normal or **Flt3-ligand**-treated mouse liver.
AU Drakes M L; Lu L; McKenna H J; Thomson A W
CS Thomas E. Starzl Transplantation Institute, University of Pittsburgh, Pennsylvania 15213, USA.
NC DK 49745-01A1 (NIDDK)
SO ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1997) 417 115-20.
Journal code: 2LU. ISSN: 0065-2598.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
EW 19980104

L3 ANSWER 9 OF 38 MEDLINE
AN 97432448 MEDLINE
DN 97432448
TI Dramatic numerical increase of functionally mature **dendritic** cells in **FLT3 ligand**-treated mice.
AU Maraskovsky E; Pulendran B; Brasel K; Teepe M; Roux E R; Shortman K; Lyman S D; McKenna H J
CS Department of Immunobiology, Immunex Corporation, Seattle, Washington 98101, USA.
SO ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1997) 417 33-40.
Ref: 35
Journal code: 2LU. ISSN: 0065-2598.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199801
EW 19980104

L3 ANSWER 10 OF 38 MEDLINE
AN 97422542 MEDLINE
DN 97422542
TI Developmental pathways of **dendritic** cells in vivo: distinct function, phenotype, and localization of **dendritic** cell subsets in **FLT3 ligand**-treated mice.
AU Pulendran B; Lingappa J; Kennedy M K; Smith J; Teepe M; Rudensky A; Maliszewski C R; Maraskovsky E
CS Immunex Corporation, Seattle, WA 98101, USA.. bpulendran@immunex.com
SO JOURNAL OF IMMUNOLOGY, (1997 Sep 1) 159 (5) 2222-31.

Journal code: IFB. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199711
EW 19971104
AB We have recently shown that **Flt3 ligand** administration dramatically increases **dendritic** cell (DC) numbers in various mouse tissues. This has enabled the identification of distinct mature DC subpopulations. These have been designated: population C (CD11c(bright) CD11b(bright)), D (CD11c(bright) CD11b(dull)), and E (CD11c(bright) CD11b(negative)) This report demonstrates that the mature DC subsets (C, D, and E) from **Flt3 ligand**-treated mice differ with respect to phenotype, geographic localization, and function. The myeloid Ags CD11b, F4/80, and Ly-6C are predominantly expressed by population C, but not D or E. In addition, a subset of population C-type DC expresses 33D1 and CD4. In contrast, DC within population D and E selectively express the lymphoid-related DC markers CD8alpha, DEC 205, CD1d, as well as CD23, elevated levels of CD117 (c-kit), CD24 (HSA), CD13, and CD54. Immunohistology indicates that the different DC subsets reside in distinct microenvironments, with populations D and E residing in the T cell areas of the white pulp, while DC within population C localize in the marginal zones. These DC subpopulations showed different capacities to phagocytose FITC-zymosan and to secrete IL-12 upon stimulation with Staphylococcus aureus cowan I strain + IFN-gamma + granulocyte-macrophage-CSF. Population C-type DC were more phagocytic but secreted little inducible IL-12 while population D- and E-type DC showed poor phagocytic capacity and secreted considerably higher levels of IL-12. These results underscore the importance of viewing DC development in vivo, as an interplay between distinct lineages and a maturational dependence on specific microenvironmental signals.

L3 ANSWER 11 OF 38 MEDLINE
AN 97415691 MEDLINE
DN 97415691
TI **FLT3 ligand** induces the generation of functionally active **dendritic** cells in mice.
AU Shurin M R; Pandharipande P P; Zorina T D; Haluszczak C; Subbotin V M; Hunter O; Brumfield A; Storkus W J; Maraskovsky E; Lotze M T
CS Biologic Therapeutics Program, University of Pittsburgh Cancer Institute, Pennsylvania 15213, USA.
NC 1PO1CA68067-01 (NCI)
SO CELLULAR IMMUNOLOGY, (1997 Aug 1) 179 (2) 174-84.
Journal code: CQ9. ISSN: 0008-8749.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199711
EW 19971104
AB **FLT3 ligand** (**FL**) is a recently described hematopoietic growth factor that stimulates the proliferation and differentiation of hematopoietic progenitors. We have investigated the effect of **FL** on murine hematopoiesis and **dendritic** cell (DC) generation and accumulation in lymphoid tissues and liver in vivo and in vitro evaluating the morphologic, phenotypic, and functional characteristics of these DC. We have observed extramedullary hematopoiesis in the mouse spleen with all lineages of hematopoietic cells represented after the administration of **FL**. Injection of **FL** results in a time-dependent and reversible accumulation of DC in the spleen,

bone marrow, lymph nodes, and liver. Both flow cytometry and immunohistochemistry revealed a significant accumulation of DC in these tissues. Results of mixed leukocyte reaction suggested that these cells, isolated from murine bone marrow or spleen, were active as antigen presenting cells. Furthermore, cultivation of splenic and marrow cells with GM-CSF and IL-4 gave rise to large numbers of functionally active mature DC. Thus, the results of this study suggest that **FL** is a promising growth factor that stimulates the generation of large number of DC and may be a useful cytokine for the immunotherapy of cancer.

L3 ANSWER 12 OF 38 MEDLINE
AN 97413635 MEDLINE
DN 97413635
TI Antitumor activity and immunotherapeutic properties of **Flt3 -ligand** in a murine breast cancer model.
AU Chen K; Braun S; Lyman S; Fan Y; Traycoff C M; Wiebke E A; Gaddy J; Sledge G; Broxmeyer H E; Cornetta K
CS Department of Medicine, Indiana University School of Medicine, Indianapolis 46202, USA.
NC PO1 CA59348 (NCI)
R01 HL54037 (NHLBI)
R01 HL56416 (NHLBI)
+
SO CANCER RESEARCH, (1997 Aug 15) 57 (16) 3511-6.
Journal code: CNF. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199711
EW 19971102
AB **Flt3-Ligand** (Flt3-L) is a stimulatory cytokine for a variety of hematopoietic lineages, including **dendritic** cells and B cells. The antitumor properties of Flt3-L were evaluated in C3H/HeN mice challenged with the syngeneic C3L5 murine breast cancer cell line. Eighty % of animals receiving 500 microg/kg/day of Chinese hamster ovary-derived human Flt3-L for 10 days were protected from tumor growth, whether the tumor challenge was administered on the first or fourth days of Flt3-L administration. The protection provided by soluble Flt3-L was transient. All tumor-free animals rechallenged 4 weeks after the primary challenge developed tumor. Transduction of C3L5 with retroviral vectors expressing human or murine Flt3-L did not influence in vitro growth or MHC expression but decreased in vivo tumor development to 0 and 10% of mice, respectively. This compares with tumor growth of 52% with interleukin-2 transduced C3L5 and over 85% with untransduced and control vector-transduced C3L5. Unlike animals treated with soluble Flt3-L, administration of Flt3-L as a tumor vaccine protected mice from a subsequent challenge with untransduced C3L5 in 60-78% of mice, compared to 0% of controls. Our initial work used the most common Flt3-L isoform, which is membrane bound but can undergo proteolytic cleavage to generate a soluble form. To evaluate the role of the various Flt3-L isoforms in preventing tumor formation, retroviral vectors encoding only the membrane-bound form or only the soluble isoform were evaluated in the C3L5 model. Tumor formation was similar with either isoform, preventing tumor formation in 80-90% of mice after the primary challenge and 88-89% after the secondary challenge. Splenocytes obtained 4 weeks after the secondary challenge conferred adoptive immunity to naive mice in 60% of animals. This initial report of antitumor activity by Flt3-L is consistent with its known stimulatory effect on antigen-presenting cells and suggests it may enhance the development of tumor vaccines.

L3 ANSWER 13 OF 38 MEDLINE
AN 97413345 MEDLINE
DN 97413345
TI **flt3 ligand** in cooperation with transforming growth factor-beta1 potentiates in vitro development of Langerhans-type **dendritic** cells and allows single-cell **dendritic** cell cluster formation under serum-free conditions.
AU Strobl H; Bello-Fernandez C; Riedl E; Pickl W F; Majdic O; Lyman S D; Knapp W
CS Institute of Immunology-Vienna International Research Cooperation Center (VIRCC) at Sandoz Forschungsinstitut (SFI), University of Vienna, Austria.
SO BLOOD, (1997 Aug 15) 90 (4) 1425-34.
Journal code: A8G. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199711
EW 19971104
AB Using a recently described serum-free culture system of purified human CD34+ progenitor cells, we show here a critical cooperation of **flt3 ligand** (**FL**) with transforming growth factor-beta1 (TGF-beta1) in the induction of in vitro **dendritic** cell/Langerhans cell (DC/LC) development. The addition of **FL** to serum-free cultures of CD34+ cells supplemented with TGF-beta1, granulocyte-macrophage colony-stimulating factor, tumor necrosis factor alpha, and stem cell factor strongly increases both percentages (mean, 36% +/- 5% v 64% +/- 4%; P = .001) and total numbers (4.4- +/- 0.8-fold) of CD1a+ **dendritic** cells. These in vitro-generated CD1a+ cells molecularly closely resemble a particular type of DC known as an epidermal Langerhans cell. Generation of DC under serum-free conditions was found to strictly require supplementation of culture medium with TGF-beta1. Upon omission of TGF-beta1, percentages of CD1a+ DC decreased (to mean, 10% +/- 8%; P = .001) and, in turn, percentages of granulomonocytic cells (CD1a- cells that are lysozyme [LZ+]; myeloperoxidase [MPO+]; CD14+) increased approximately threefold (P < .05). Furthermore, in the absence of TGF-beta1, **FL** consistently promotes generation of LZ+, MPO+, and CD14+ cells, but not of CD1a+ cells. Serum-free single-cell cultures set up under identical TGF-beta1- and **FL**-supplemented culture conditions showed that high percentages of CD34+ cells (mean, 18% +/- 2%; n = 4) give rise to day-10 DC colony formation. The majority of cells in these DC-containing colonies expressed the Langerhans cell/Birbeck granule specific marker molecule Lag. Without TGF-beta1 supplementation, Lag+ colony formation is minimal and formation of monocyte/macrophage-containing colonies predominates. Total cloning efficiency in the absence and presence of TGF-beta1 is virtually identical (mean, 41% +/- 6% v 41% +/- 4%). Thus, **FL** has the potential to strongly stimulate DC/LC generation, but has a strict requirement for TGF-beta1 to show this costimulatory effect.

L3 ANSWER 14 OF 38 MEDLINE
AN 97351065 MEDLINE
DN 97351065
TI Chronic expression of murine **flt3 ligand** in mice results in increased circulating white blood cell levels and abnormal cellular infiltrates associated with splenic fibrosis.
AU Juan T S; McNiece I K; Van G; Lacey D; Hartley C; McElroy P; Sun Y; Argento J; Hill D; Yan X Q; Fletcher F A
CS Department of Developmental Hematology, Amgen, Inc, Thousand Oaks, CA 93012-1789, USA.
SO BLOOD, (1997 Jul 1) 90 (1) 76-84.

Journal code: A8G. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199709
EW 19970904
AB The effect of chronic expression of **flt3 ligand** (**FL**) on in vivo hematopoiesis was studied. Retroviral vector-mediated gene transfer was used in a mouse model of bone marrow transplantation to enforce expression of mouse **FL** cDNA in hematopoietic tissues. As early as 2 weeks posttransplantation, peripheral blood white blood cell counts in **FL**-overexpressing recipients were significantly elevated compared with controls. With the exception of eosinophils, all nucleated cell lineages studied were similarly affected in these animals. Experimental animals also exhibited severe anemia and progressive loss of marrow-derived erythropoiesis. All of the **FL**-overexpressing animals, but none of the controls, died between 10 and 13 weeks posttransplantation. Upon histological examination, severe splenomegaly was noted, with progressive fibrosis and infiltration by abnormal lymphoreticular cells. Abnormal cell infiltration also occurred in other organ systems, including bone marrow and liver. In situ immunocytochemistry on liver sections showed that the cellular infiltrate was CD3+/NLDC145+/CD11c+, but B220- and F4/80-, suggestive of a mixed infiltrate of **dendritic** cells and activated T lymphocytes. Infiltration of splenic blood vessel perivascular spaces resulted in vascular compression and eventual occlusion, leading to splenic necrosis consistent with infarction. These results show that **FL** can affect both myeloid and lymphoid cell lineages in vivo and further demonstrate the potential toxicity of in vivo treatment with **FL**.

L3 ANSWER 15 OF 38 MEDLINE
AN 97319585 MEDLINE
DN 97319585
TI **Flt3 ligand** induces tumor regression and antitumor immune responses in vivo.
AU Lynch D H; Andreasen A; Maraskovsky E; Whitmore J; Miller R E; Schuh J C
CS Department of Immunobiology, Immunex Corporation, Seattle, Washington 98101, USA.
SO NATURE MEDICINE, (1997 Jun) 3 (6) 625-31.
Journal code: CG5. ISSN: 1078-8956.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199709
EW 19970902
AB Daily treatment of mice with recombinant human **Flt3 ligand** (huFlt3L) results in a dramatic numerical increase in the number of **dendritic** cells (DCs) in vivo. Since DCs are pivotal in the induction of immune responses, we tested whether Flt3L treatment of mice challenged with a syngeneic methylcholanthrene (MCA)-induced fibrosarcoma would augment the generation of effective antitumor immune responses in vivo. Flt3L treatment not only induced complete tumor regression in a significant proportion of mice, but also decreased tumor growth rate in the remaining mice. A preliminary characterization of the cellular mechanisms involved suggests that Flt3L may be important in the treatment of cancer in situ through the generation of specific antitumor immune responses.

L3 ANSWER 16 OF 38 MEDLINE
AN 97301607 MEDLINE
DN 97301607
TI Striking augmentation of hematopoietic cell chimerism in noncytoablated allogeneic bone marrow recipients by **FLT3 ligand** and tacrolimus.
AU Iyengar A R; Bonham C A; Antonysamy M A; Subbotin V M; Khanna A; Murase N; Rao A S; Starzl T E; Thomson A W
CS Thomas E. Starzl Transplantation Institute and Department of Surgery, University of Pittsburgh, Pennsylvania 15213, USA.
NC DK 49745 (NIDDK)
DK 29961 (NIDDK)
SO TRANSPLANTATION, (1997 May 15) 63 (9) 1193-9.
Journal code: WEJ. ISSN: 0041-1337.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199708
EW 19970802
AB The influence of granulocyte-macrophage colony-stimulating factor (GM-CSF) and the recently identified hematopoietic stem-progenitor cell mobilizing factor **flt3 ligand** (**FL**) on donor leukocyte microchimerism in noncytodepleted recipients of allogeneic bone marrow (BM) was compared. B10 mice (H2b) given 50x10(6) allogeneic (B10.BR [H2k]) BM cells also received either GM-CSF (4 microg/day s.c.), **FL** (10 microg/day i.p.), or no cytokine, with or without concomitant tacrolimus (formerly FK506; 2 mg/kg) from day 0. Chimerism was quantitated in the spleen 7 days after transplantation by both polymerase chain reaction (donor DNA [major histocompatibility complex class II; I-E(k)]) and immunohistochemical (donor [I-E(k)+] cell) analyses. Whereas GM-CSF alone significantly augmented (fivefold) the level of donor DNA in recipients' spleens, **FL** alone caused a significant (60%) reduction. Donor DNA was increased 10-fold by tacrolimus alone, whereas coadministration of GM-CSF and tacrolimus resulted in a greater than additive effect (28-fold increase). A much more striking effect was observed with **FL** + tacrolimus (>125-fold increase in donor DNA compared with BM alone). These findings were reflected in the relative numbers of donor major histocompatibility complex class II+ cells (many resembling **dendritic** cells) detected in spleens, although quantitative differences among the groups were less pronounced. Evaluation of cytotoxic T lymphocyte generation by BM recipients' spleen cells revealed that **FL** alone augmented antidonor immunity and that this was reversed by tacrolimus. Thus, although **FL** may potentiate antidonor reactivity in nonimmunosuppressed, allogeneic BM recipients, it exhibits potent chimerism-enhancing activity when coadministered with recipient immunosuppressive therapy.

L3 ANSWER 17 OF 38 MEDLINE
AN 97248393 MEDLINE
DN 97248393
TI Human immunodeficiency virus type 1 infection of cells and tissues from the upper and lower human female reproductive tract.
AU Howell A L; Edkins R D; Rier S E; Yeaman G R; Stern J E; Fanger M W; Wira C R
CS Department of Veterans Affairs, White River Junction, Vermont 05009, USA.. alexandra.howell@dartmouth.EDU
NC AI 34478 (NIAID)
CA 23108 (NCI)
SO JOURNAL OF VIROLOGY, (1997 May) 71 (5) 3498-506.
Journal code: KCV. ISSN: 0022-538X.
CY United States

DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199707
EW 19970701
AB Viable tissue sections and isolated cell cultures from the human fallopian tube, uterus, cervix, and vaginal mucosa were examined for susceptibility to infection with human immunodeficiency virus type 1 (HIV-1). We examined infectivity by using the monocytotropic strain HIV-1(JR-**FL**) and several primary isolates of HIV-1 obtained from infected neonates. HIV-1 infection was measured by p24 production in short-term culture and by immunofluorescence detection of HIV-1 Nef and p24 proteins by laser scanning confocal microscopy. Three-color immunofluorescence was used to phenotype HIV-infected cells within tissue sections from each site. Our findings indicate that epithelial, stromal, and **dendritic** cells and cells with CD14+ CD4+, CD14-CD4-, and CD4+ CD14- phenotypes from the female reproductive tract are infectable with HIV-1. Of importance is the finding that tissues from the upper reproductive tract are susceptible to infection with HIV-1. Moreover, tissue samples from women in all stages of the menstrual cycle, including postmenopausal women (inactive), could be infected with HIV-1. Female reproductive tract cells required a minimum of 60 min of exposure to HIV-1 in order for infection to occur, in contrast to peripheral blood lymphocytes, which became infected after being exposed to HIV-1 for only 1 min. These findings demonstrate that HIV-1 can infect cells and tissues from different sites within the female reproductive tract and suggest that multiple cell types, including epithelial cells, may be targets for the initial infection by HIV-1.

L3 ANSWER 18 OF 38 MEDLINE
AN 97179619 MEDLINE
DN 97179619
TI Nerve growth factor treatment prevents **dendritic** atrophy and promotes recovery of function after cortical injury.
AU Kolb B; Cote S; Ribeiro-da-Silva A; Cuello A C
CS Department of Psychology, University of Lethbridge, Canada.
SO NEUROSCIENCE, (1997 Feb) 76 (4) 1139-51.
Journal code: NZR. ISSN: 0306-4522.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199707
EW 19970701
AB This study examined the behavioural and anatomical effects of intraventricular injections of nerve growth factor in rats with unilateral damage that included Zilles' areas Frl, **FL**, HL, ParI and the anterior portion of Oc2. Nerve growth factor-treated lesion rats showed attenuation of behavioural symptoms in measures of forelimb function (Whishaw reaching task) and hindlimb function (beam traversing task) as well as a measure of spatial navigation (Morris water task). Analysis of **dendritic** arborization using a modified Golgi. Cox procedure also showed a complete reversal of lesion-induced atrophy of **dendritic** fields in pyramidal neurons in motor (Zilles' Fr2) and cingulate (Zilles' Cg1) cortex. In addition, there was a reversal of a lesion-induced reduction in spine density. These results demonstrate that nerve growth factor treatment can facilitate functional recovery from cortical injury. This recovery may be mediated by a reorganization of intrinsic cortical circuitry that is reflected in changes in **dendritic** arborization and spine density of pyramidal neurons.

L3 ANSWER 19 OF 38 MEDLINE

AN 97079150 MEDLINE
DN 97079150
TI Dramatic increase in the numbers of functionally mature **dendritic** cells in **Flt3 ligand**-treated mice: multiple **dendritic** cell subpopulations identified.
AU Maraskovsky E; Brasel K; Teepe M; Roux E R; Lyman S D; Shortman K; McKenna H J
CS Department of Immunobiology, Immunex Corporation, Seattle, Washington 98101, USA.
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1996 Nov 1) 184 (5) 1953-62. Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199703
EW 19970301
AB **Dendritic** cells (DC) are the most efficient APC for T cells. The clinical use of DC as vectors for anti-tumor and infectious disease immunotherapy has been limited by their trace levels and accessibility in normal tissue and terminal state of differentiation. In the present study, daily injection of human **Flt3 ligand** (Flt3L) into mice results in a dramatic numerical increase in cells co-expressing the characteristic DC markers-class II MHC, CD11c, DEC205, and CD86. In contrast, in mice treated with either GM-CSF, GM-CSF plus IL-4, c-kit ligand (c-kitL), or G-CSF, class II+ CD11c+ cells were not significantly increased. Five distinct DC subpopulations were identified in the spleen of Flt3L-treated mice using CD8 alpha and CD11b expression. These cells exhibited veiled and **dendritic** processes and were as efficient as rare, mature DC isolated from the spleens of untreated mice at presenting allo-Ag or soluble Ag to T cells, or in priming an Ag-specific T cell response in vivo. Dramatic numerical increases in DC were detected in the bone marrow, gastro-intestinal lymphoid tissue (GALT), liver, lymph nodes, lung, peripheral blood, peritoneal cavity, spleen, and thymus. These results suggest that Flt3L could be used to expand the numbers of functionally mature DC in vivo for use in clinical immunotherapy.

L6 ANSWER 1 OF 24 MEDLINE
AN 97426675 MEDLINE
DN 97426675
TI Peptide epitope mapping in vaccine development: introduction.
AU Castric P A; Cassels F J
CS Department of Biological Sciences, Duquesne University, Pittsburgh, PA 15282, USA.
SO J Ind Microbiol Biotechnol, (1997 Jul) 19 (1) 56-7.
Journal code: CTU. ISSN: 1367-5435.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; B
EM 199711
EW 19971103
AB Protection from **infectious disease** by the host immune response requires specific molecular recognition of unique antigenic determinants of a given pathogen. An epitope is an antigenic determinant which: 1) specifically stimulates the immune response (either B or T cell mediated); and 2) is acted upon by the products of these protective mechanisms. In B cell immunity, antibodies produced from stimulation by specific epitopes recognize and bind to these same antigenic structures. Identification of protective epitopes is extremely valuable to successful vaccine development. In order to be protective these antibodies must, in addition to recognition and binding, interfere with some vital step in pathogenesis such as adherence or toxin action. Protein B cell epitopes are frequently composed of the side chains (R-groups) of the amino acids found at solvent-exposed surfaces. These epitopes are classified as continuous (also linear or sequential) if composed of a single antibody-recognizing element located at a single locus of the primary structure. They are discontinuous (or assembled) if more than one physically separated entity is involved. T cell epitopes are peptides on the surface of antigen-presenting cells (macrophages, **dendritic** cells, and B cells) that are bound to major histocompatibility proteins; the T cell recognizes this peptide-MHC complex.

L6 ANSWER 2 OF 24 MEDLINE
AN 97196360 MEDLINE
DN 97196360
TI Function and clinical use of interleukin-12.
AU Trinchieri G
CS Wistar Institute of Anatomy and Biology, Philadelphia, PA 19104, USA.
SO Curr Opin Hematol, (1997 Jan) 4 (1) 59-66. Ref: 78
Journal code: CN0. ISSN: 1065-6251.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199705
EW 19970505
AB Interleukin-12 is a heterodimeric cytokine produced by phagocytic cells, professional antigen-presenting cells such as **dendritic** cells and skin Langerhans cells, and B cells.

Interleukin-12 production is induced by bacteria, intracellular pathogens, fungi, viruses, or their products in a T-cell-independent pathway or a T-cell-dependent pathway, the latter mediated through CD40 ligand-CD40 interaction. Interleukin-12 is produced rapidly after infection and acts as a proinflammatory cytokine eliciting production of interferon gamma, by T and natural killer cells, which activates phagocytic cells. The production of interleukin-12 is strictly regulated by positive and negative feedback mechanisms. If interleukin-12 and interleukin-12-induced interferon gamma are present during early T-cell expansion in response to antigen, T-helper type-1 cell generation is favored and generation of T-helper type-2 cells is inhibited. Thus interleukin-12 is also a potent immunoregulatory cytokine that promotes T-helper type-1 differentiation and is instrumental in the T-helper type-1-dependent resistance to infections by bacteria, intracellular parasites, fungi, and certain viruses. By inhibiting T-helper type-2 cell response, interleukin-12 has a suppressive effect on allergic reactions; by promoting T-helper type-1 responses it participates in the immunopathology responsible for several organ-specific autoimmune diseases. Viruses inducing a permanent or transient immunodepression, such as HIV and measles, may act, in part, by suppressing interleukin-12 production. Because of its ability to enhance resistance to several **infectious diseases** and to act as an adjuvant in vaccination, and because of its powerful antitumor effect in vivo, interleukin-12 is currently in clinical trials in cancer patients and HIV-infected patients, and it is being considered for therapeutic use in other diseases.

L6 ANSWER 3 OF 24 MEDLINE
AN 97079150 MEDLINE
DN 97079150
TI Dramatic increase in the numbers of functionally mature **dendritic** cells in Flt3 ligand-treated mice: multiple **dendritic** cell subpopulations identified.
AU Maraskovsky E; Brasel K; Teepe M; Roux E R; Lyman S D; Shortman K; McKenna H J
CS Department of Immunobiology, Immunex Corporation, Seattle, Washington 98101, USA.
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1996 Nov 1) 184 (5) 1953-62. Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199703
EW 19970301
AB **Dendritic** cells (DC) are the most efficient APC for T cells. The clinical use of DC as vectors for anti-tumor and **infectious disease** immunotherapy has been limited by their trace levels and accessibility in normal tissue and terminal state of differentiation. In the present study, daily injection of human Flt3 ligand (Flt3L) into mice results in a dramatic numerical increase in cells co-expressing the characteristic DC markers-class II MHC, CD11c, DEC205, and CD86. In contrast, in mice treated with either GM-CSF, GM-CSF plus IL-4, c-kit ligand (c-kitL), or G-CSF, class II+ CD11c+ cells were not significantly increased. Five distinct DC subpopulations were identified in the spleen of Flt3L-treated mice using CD8 alpha and CD11b expression. These cells exhibited veiled and **dendritic** processes and were as efficient as rare, mature DC isolated from the spleens of untreated mice at presenting allo-Ag or soluble Ag to T cells, or in priming an Ag-specific T cell response in vivo. Dramatic numerical increases in DC were detected in the bone marrow, gastro-intestinal lymphoid tissue (GALT), liver, lymph nodes, lung, peripheral blood, peritoneal cavity, spleen, and thymus. These

results suggest that Flt3L could be used to expand the numbers of functionally mature DC in vivo for use in clinical immunotherapy.

L6 ANSWER 4 OF 24 MEDLINE
AN 96404985 MEDLINE
DN 96404985
TI **Dendritic** cells and tolerance induction.
AU Steptoe R J; Thomson A W
CS Pittsburgh Transplantation Institute, University of Pittsburgh, PA 15213, USA.
NC RO1DK49745-10A1 (NIDDK)
SO CLINICAL AND EXPERIMENTAL IMMUNOLOGY, (1996 Sep) 105 (3) 397-402.
Ref: 91
Journal code: DD7. ISSN: 0009-9104.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals; Cancer Journals
EM 199701
EW 19970104
AB **Dendritic** cells (DC) are widely accepted as the most potent antigen-presenting cells (APC), and considerable interest has been generated in their potential for the immunological therapy of cancer and **infectious disease**. Recently, however, a broader understanding of the phenotypic diversity and functional heterogeneity of DC has been acquired. Thus, in addition to having a role in central tolerance, DC are now regarded as potential modulators of peripheral immune responses. Harnessing this potential may offer a new approach to the immunosuppressive therapy of allograft rejection or autoimmunity. Here, the concept of "tolerogenic" DC is placed in the context of rapidly accumulating new evidence of the diverse properties of these important APC.

L6 ANSWER 5 OF 24 MEDLINE
AN 96253916 MEDLINE
DN 96253916
TI [Mechanisms involved in the prolonged humoral immune response: behavior of aphthous fever virus].
Mecanismos involucrados en la respuesta inmune humoral prolongada: comportamiento del virus de la fiebre aftosa.
AU Wigdorovitz A; Sadir A
CS Centro de Investigacion en Ciencias Veterinarias, Instituto Nacional de Tecnologia Agropecuaria (INTA), Argentina.
SO REVISTA ARGENTINA DE MICROBIOLOGIA, (1996 Jan-Mar) 28 (1) 45-54.
Ref: 45
Journal code: QZ8. ISSN: 0325-7541.
CY Argentina
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA Spanish
FS Priority Journals
EM 199612
AB Foot and mouth disease (FMD) is a widespread **infectious disease** affecting cloven-hoofed animals with severe economic consequences. Animals infected with FMD virus (FMDV) develop an immunological status of immunity characterized by high titers of virus serotype-specific neutralizing antibodies (NAb) which persist for at least 18 months. In contrast, currently inactivated virus vaccines elicit lower antibody response for shorter periods. Protection against FMDV infection has been commonly related to the level of NAb in serum. The new generation vaccines are immunologically poor, and for this reason it is important that the

immunological mechanisms are activated during the infection to potentiate the action of these vaccines. The objective of this review is to present the possible mechanisms involved in the long lasting humoral immune response after FMDV infection. The necessity of the Ag for the initiation of the response is well known, although its role in maintaining and regulating the immune response is still unclear. The continuous role of the Ag in maintaining the response was demonstrated in experiments in which Abs with different specificities for long periods of time without the administration of exogen Ag were detected. The capture and retention of Ab-Ag complex by **dendritic** follicular cells seems to be a important factor in the increase of the Ag production and in the generation of B memory cells. The genomic persistence is strongly related to the Ag persistence. During a persistent infection, in which the genome is maintained and able to synthesize proteins, the immune system would be continuously stimulated. The continuous liberation of soluble Ag, as a productive persistent infection, induces the B cells memory for its differentiation in Abs producing cells. The antigen presenting cells (APC) are cells which present the Ag to lymphocytes in the class II MHC context. Langerhans islets, **dendritic**, B and phagocytic cells form the APC group. The modulation of the function of the APC cells is very important in the self regulation of the immune system. The function on the immune response depends on the capacity of generating signals for the stimulation of T cells.

L6 ANSWER 6 OF 24 MEDLINE
AN 96164567 MEDLINE
DN 96164567
TI Class II MHC antigen (Ia)-bearing **dendritic** cells in the epithelium of the rat intestine.
AU Maric I; Holt P G; Perdue M H; Bienenstock J
CS Department of Pathology, McMaster University, Hamilton, Ontario, Canada.
SO JOURNAL OF IMMUNOLOGY, (1996 Feb 15) 156 (4) 1408-14.
Journal code: IFB. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199605
AB Many tissues are found to contain populations of cells with an unusual **dendritic** shape, high levels of surface expression of MHC class II (Ia) gene products, and strong accessory function for the stimulation of specific clones of quiescent T lymphocytes. **Dendritic** cells (DC) represent major population of "professional" APC in various lymphoid and nonlymphoid tissues, distinct from cells of the monocyte/macrophage lineage. Among the best characterized nonlymphoid **dendritic** cells are epidermal Langerhans cells, but it has been shown that interstitium and epithelium of other organs also contain irregularly shaped, strongly MHC class II positive cells. In recent years, DC have been localized to alveolar septa in the lung, as well as within and just beneath airway epithelium, comprising a tightly meshed network that is reminiscent of epidermal Langerhans cells. In the gastrointestinal tract, conventional immunohistochemical analysis of mucosal class II MHC (Ia) staining reveals a morphologically heterogeneous pattern of staining in the lamina propria. DC that exhibit strong Ag-presenting activity in vitro have been extracted from enzymatic digests of colonic mucosa, but no previous reports of MHC class II-positive cells with pleiomorphic morphology have been recorded within the epithelium of the intestine. Employing a novel combination of nonconventional section planes, pre-embedding fixation, and immunohistochemical techniques, we now demonstrate Ia staining of cells with classical DC morphology within the epithelium

of the intestine in normal specific pathogen-free rats. Our investigation suggests that cells with the morphologic and phenotypical characteristics of DC are present within the mucosal epithelium of the rat jejunum and colon, comprising a significant organized network. The number of DC within epithelium of the colon was 117 +/- 20 per 10-microns-thick cross-section. These findings have important theoretical implications for research on Ag processing and T cell activation in the context of allergic and **infectious diseases** in the gastrointestinal tract.

L6 ANSWER 7 OF 24 MEDLINE
AN 95310858 MEDLINE
DN 95310858
TI Bone marrow-generated **dendritic** cells pulsed with a class I-restricted peptide are potent inducers of cytotoxic T lymphocytes.
AU Porgador A; Gilboa E
CS Department of Surgery, Duke University Medical Center, Durham, North Carolina 27710, USA.
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1995 Jul 1) 182 (1) 255-60. Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199509
AB It has previously been shown that bone marrow-generated **dendritic** cells (DC) are potent stimulators in allogeneic mixed leukocyte reactions and are capable of activating naive CD4+ T cells in situ in an antigen-specific manner. In this study we have investigated whether bone marrow-generated DC are capable of inducing antigen-specific CD8+ T cell responses in vivo. Initial attempts to induce specific cytotoxic T lymphocyte (CTL) responses in mice injected with bone marrow-generated DC pulsed with ovalbumin (OVA) peptide were frustrated by the presence of high levels of nonspecific lytic activity, which obscured, though not completely, the presence of Ag-specific CTL. Using conditions that effectively differentiate between antigen-specific and nonspecific lytic activity, we have shown that bone marrow-generated DC pulsed with OVA peptide are potent inducers of OVA-specific CTL responses in vivo, compared with splenocytes or RMA-S cells pulsed with OVA peptide, or compared with immunization with free OVA peptide mixed with adjuvant. Antibody-mediated depletion experiments have shown that the cytotoxic effector cells consist primarily of CD8+ cells, and that induction of CTL in vivo is dependent on CD4+ as well as on CD8+ T cells. These results provide the basis for exploring the role of bone marrow-generated DC in major histocompatibility class I-restricted immune responses, and they provide the rationale for using bone marrow-generated DC in CTL-mediated immunotherapy of cancer and **infectious diseases**.

L6 ANSWER 8 OF 24 MEDLINE
AN 95193813 MEDLINE
DN 95193813
TI Hantavirus pulmonary syndrome. Pathogenesis of an emerging **infectious disease**.
AU Zaki S R; Greer P W; Coffield L M; Goldsmith C S; Nolte K B; Foucar K; Feddersen R M; Zumwalt R E; Miller G L; Khan A S; et al
CS Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30333..
SO AMERICAN JOURNAL OF PATHOLOGY, (1995 Mar) 146 (3) 552-79. Journal code: 3RS. ISSN: 0002-9440.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 199506
AB A recent outbreak of a severe pulmonary disease in the southwestern United States was etiologically linked to a previously unrecognized hantavirus. The virus has been isolated from its major reservoir, the deer mouse, Peromyscus maniculatus, and recently named Sin Nombre virus. Clinically, the disease has become known as the hantavirus pulmonary syndrome (HPS). Since May 1993, 44 fatal cases of HPS have been identified through clinicopathological review and immunohistochemical (IHC) testing of tissues from 273 patients who died of an unexplained noncardiogenic pulmonary edema. In 158 cases for which suitable specimens were available, serological testing and/or reverse transcription-polymerase chain reaction (RT-PCR) amplification of extracted RNA was also performed. IHC, serological, and PCR results were concordant for virtually all HPS and non-HPS patients when more than one assay was performed. The prodromal illness of HPS is similar to that of many other viral diseases. Consistent hematological features include thrombocytopenia, hemoconcentration, neutrophilic leukocytosis with a left shift, and reactive lymphocytes. Pulmonary histopathological features were similar in most of the fatal HPS cases (40/44) and consisted of an interstitial pneumonitis with a variable mononuclear cell infiltrate, edema, and focal hyaline membranes. In four cases, however, pulmonary features were significantly different and included diffuse alveolar damage and variable degrees of severe air space disorganization. IHC analysis showed widespread presence of hantaviral antigens in endothelial cells of the microvasculature, particularly in the lung. Hantaviral antigens were also observed within follicular **dendritic** cells, macrophages, and lymphocytes. Hantaviral inclusions were observed in endothelial cells of lungs by thinsection electron microscopy, and their identity was verified by immunogold labeling. Virus-like particles were seen in pulmonary endothelial cells and macrophages. HPS is a newly recognized, often fatal disease, with a spectrum of microscopic morphological changes, which may be an important cause of severe and fatal illness presenting as adult respiratory distress syndrome.

L6 ANSWER 9 OF 24 MEDLINE
AN 94095915 MEDLINE
DN 94095915
TI Zanvil Alexander Cohn 1926-1993.
AU Steinman R M; Moberg C L
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1994 Jan 1) 179 (1) 1-30.
Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Bibliography
Biography
Historical
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199404
AB Zanvil Alexander Cohn, an editor of this Journal since 1973, died suddenly on June 28, 1993. Cohn is best known as the father of the current era of macrophage biology. Many of his scientific accomplishments are recounted here, beginning with seminal studies on the granules of phagocytes that were performed with his close colleague and former editor of this Journal, James Hirsch. Cohn and Hirsch identified the granules as lysosomes that discharged their contents of digestive enzymes into vacuoles containing phagocytosed microbes. These findings were part of the formative era of cell biology and initiated the modern study of endocytosis and cell-mediated resistance to infection. Cohn further explored the endocytic apparatus in pioneering studies of the mouse peritoneal macrophage in culture. He described vesicular inputs from the cell

surface and Golgi apparatus and documented the thoroughness of substrate digestion within lysosomal vacuoles that would only permit the egress of monosaccharides and amino acids. These discoveries created a vigorous environment for graduate students, postdoctoral fellows, and junior and visiting faculty. Some of the major findings that emerged from Cohn's collaborations included the radioiodination of the plasma membrane for studies of composition and turnover; membrane recycling during endocytosis; the origin of the mononuclear phagocyte system in situ; the discovery of the **dendritic** cell system of antigen-presenting cells; the macrophage as a secretory cell, including the release of proteases and large amounts of prostaglandins and leukotrienes; several defined parameters of macrophage activation, especially the ability of T cell-derived lymphokines to enhance killing of tumor cells and intracellular protozoa; the granule discharge mechanism whereby cytotoxic lymphocytes release the pore-forming protein perforin; the signaling of macrophages via myristoylated substrates of protein kinase C; and a tissue culture model in which monocytes emigrate across tight endothelial junctions. In 1983, Cohn turned to a long-standing goal of exploring host resistance directly in humans. He studied leprosy, focusing on the disease site, the parasitized macrophages of the skin. He injected recombinant lymphokines into the skin and found that these molecules elicited several cell-mediated responses. Seeing this potential to enhance host defense in patients, Cohn was extending his clinical studies to AIDS and tuberculosis. Zanvil Cohn was a consummate physician-scientist who nurtured the relationship between cell biology and **infectious disease** .(ABSTRACT TRUNCATED AT 400 WORDS)

L6 ANSWER 10 OF 24 MEDLINE
AN 93378331 MEDLINE
DN 93378331
TI Tolerance and ways to break it.
AU Nossal G J
CS Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital, Victoria, Australia..
NC AI-03958 (NIAID)
SO ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1993 Aug 12) 690 34-41.
Ref: 29
Journal code: 5NM. ISSN: 0077-8923.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals; Cancer Journals
EM 199312
AB The overall picture as regards cellular mechanisms in immunologic tolerance is thus clear. Thymic negative selection is an important and dominant mechanism for both CD4+ and CD8+ T cells for those antigens (and they may be very many indeed), the peptides of which get expressed within the thymus. The induction of anergy among peripheral T lymphocytes may represent an ancillary mechanism in some cases, but this is not as clear as it appeared 2 or 3 years ago. Evidently, in many cases, T cells simply ignore antigens present only within specialized organs, and these T cells, even if only of low affinity for the antigen in question, could be provoked into autoimmunity if sufficient help is provided, for example, through localized production of IL-2 or through provision of cross-reactive help. B-cell tolerance is also proven and involves deletional mechanisms (most likely maturation arrest) or functional inactivation (clonal anergy). The former phenomenon dominates for self-antigens that strongly cross-link the B cell's Ig receptors and the latter for weaker negative signals. Despite these two mechanisms, clonal ignorance prevails for many self-antigens. The

secondary B-cell repertoire is also largely free of anti-self B cells, lack of T-cell help being a major factor in preventing the development of anti-self memory B cells. Therefore, to have the best chance of creating an immunogenic antitumor vaccine, a few simple and rather obvious rules must be followed. The antigen in question must be presented in such a way as to be palatable to "professional" antigen-presenting cells, particularly **dendritic** cells and macrophages. Immunotherapy protocols should avoid at all costs the widespread distribution of the antigen in question through the extracellular fluids. Indeed, it is possible that widespread circulation of a tumor-associated antigen through the serum and lymph because of large-scale shedding from the tumor cell may already have created a substantial degree of tolerance to the antigen in question in both T- and B-cell populations. If that has happened, it becomes particularly important to create a cancer vaccine capable of inducing help. This may well involve coupling of the most important epitopes to some highly immunogenic and foreign carrier. A wide choice of adjuvants is available for the designer of tumor vaccines, and in this regard the cancer immunotherapy community has much to learn from the rapidly developing field of **infectious disease** vaccinology using recombinant and other vaccines.(ABSTRACT TRUNCATED AT 400 WORDS)

L6 ANSWER 11 OF 24 MEDLINE
AN 93356629 MEDLINE
DN 93356629
TI Role of Langerhans cells and other **dendritic** cells in viral diseases.
AU Sprecher E; Becker Y
CS Department of Molecular Virology, Faculty of Medicine, Hebrew University, Jerusalem, Israel..
SO ARCHIVES OF VIROLOGY, (1993) 132 (1-2) 1-28. Ref: 157
Journal code: 8L7. ISSN: 0304-8608.
CY Austria
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals; Cancer Journals
EM 199311
AB Langerhans cells are part of a vast system of potent antigen-presenting cells known under the name of **dendritic** cells. During the last decade, much has been learned on **dendritic** cell involvement in the immune response to **infectious diseases**. This review briefly summarizes our current understanding of the role played by Langerhans cells and other **dendritic** cells in the pathogenesis of DNA and RNA virus infections. These data may form the basis for the development of innovative approaches in the diagnosis, prevention, and treatment of viral diseases.

L6 ANSWER 12 OF 24 MEDLINE
AN 93048014 MEDLINE
DN 93048014
TI Delayed onset of varicella keratitis.
AU de Freitas D; Sato E H; Kelly L D; Pavan-Langston D
CS Department of Ophthalmology, Harvard Medical School, Boston, MA..
NC EY06584 (NEI)
SO CORNEA, (1992 Sep) 11 (5) 471-4. Ref: 34
Journal code: DSN. ISSN: 0277-3740.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW OF REPORTED CASES)
LA English

FS Priority Journals
EM 199302
AB Although varicella is one of the most common **infectious diseases** in the United States, systemic and ocular complications are rare. We report a patient who developed disciform edema followed by microdendritic keratitis 1 and 2 months, respectively, after resolution of the acute phase of varicella. Cultures were negative, but serologic analysis found positive antibodies against varicella zoster virus and negative antibodies against herpes simplex virus. Based on this case and on a review of the literature, we believe that this delayed onset of keratitis represents a distinct category of varicella corneal complications.

L6 ANSWER 13 OF 24 MEDLINE
AN 91237282 MEDLINE
DN 91237282
TI Studies on the density, distribution, and surface phenotype of intraepithelial class II major histocompatibility complex antigen (Ia)-bearing **dendritic** cells (DC) in the conducting airways.
AU Schon-Hegrad M A; Oliver J; McMenamin P G; Holt P G
CS Division of Cell Biology, Western Australian Research Institute for Child Health, Princess Margaret Hospital, Subiaco..
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1991 Jun 1) 173 (6) 1345-56. Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199108
AB Conventional immunohistochemical analysis of airway intraepithelial class II major histocompatibility complex (Ia) expression demonstrates a morphologically heterogeneous pattern of staining, suggestive of the presence of a mixed population of endogenous antigen presenting cells. Employing a novel tissue sectioning technique in conjunction with optimal surface antigen fixation, we now demonstrate that virtually all intraepithelial Ia staining throughout the respiratory tree in the normal rat, can be accounted for by a network of cells with classical **dendritic** cell (DC) morphology. The density of DC varies from 600-800 per mm2 epithelial surface in the large airways, to 75 per mm2 in the epithelium of the small airways of the peripheral lung. All the airway DC costain for CD4, with low-moderate expression of a variety of other leukocyte surface markers. Both chronic (eosinophilic) inflammation and acute (neutrophilic) inflammation, caused respectively by inhalation of chemical irritants in dust or aerosolised bacterial lipopolysaccharide (LPS), are shown to be accompanied by increased intraepithelial DC density in the large airways (in the order of 50%) and up to threefold increased expression of activation markers, including the beta chain of CD11/18. The kinetics of the changes in the DC network in response to LPS mirrored those of the transient neutrophil influx, suggesting that airway intraepithelial DC constitute a dynamic population which is rapidly upregulated in response to local inflammation. These findings have important theoretical implications for research on T cell activation in the context of allergic and **infectious diseases** in the respiratory tract.

L6 ANSWER 14 OF 24 MEDLINE
AN 90256307 MEDLINE
DN 90256307
TI A contiguous network of **dendritic** antigen-presenting cells within the respiratory epithelium.
AU Holt P G; Schon-Hegrad M A; Oliver J; Holt B J; McMenamin P G
CS Clinical Immunology Research Unit, Children's Medical Research

Foundation, Princess Margaret Hospital, Perth, Australia..
SO INTERNATIONAL ARCHIVES OF ALLERGY AND APPLIED IMMUNOLOGY, (1990) 91 (2) 155-9.
Journal code: GP9. ISSN: 0020-5915.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199008
AB This study utilises a simple technique to section airway epithelium in a plane parallel to the basement membrane, thus providing a unique plan view of the intra-epithelial cell populations. Immunoperoxidase staining of these tissue sections for class II major histocompatibility complex Ia antigen reveals a virtually contiguous network of Ia-positive **dendritic** cells (DC) within the epithelium. These DC are shown to be capable of binding inhaled antigens in vivo in a form suitable for presentation to T cells. The strategic location of these cells and the fact that they account for virtually all staining in the airway epithelium during the steady state is convincing evidence that the DC network functions as the 'first line of defence' in surveillance for inhaled antigens and further suggests a major role for the intra-epithelial DC in allergic and **infectious disease**(s) in the respiratory tract.

L6 ANSWER 15 OF 24 MEDLINE
AN 90090218 MEDLINE
DN 90090218
TI Ia-positive **dendritic** cells form a tightly meshed network within the human airway epithelium.
AU Holt P G; Schon-Hegrad M A; Phillips M J; McMenamin P G
CS Clinical Immunology Research Unit, Princess Margaret Hospital, Subiaco, Western Australia..
SO CLINICAL AND EXPERIMENTAL ALLERGY, (1989 Nov) 19 (6) 597-601.
Journal code: CEB. ISSN: 0954-7894.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199004
AB In this report we have employed an alternative tissue-sectioning procedure which provides a plan view of intra-epithelial cell populations within the airway wall. Immunoperoxidase staining of such sections for class II MHC (Ia) antigen revealed the presence of a highly developed intra-epithelial network of Ia-positive **dendritic** cells, which was not evident employing conventional cross- or longitudinal tissue sections. This finding has important implications for the study of mechanisms underlying allergic and **infectious diseases** of the respiratory tract.

L10 ANSWER 20 OF 23 BIOSIS COPYRIGHT 1998 BIOSIS
AN 91:124580 BIOSIS
DN BR40:56265
TI SOME THOUGHTS ON THE FUTURE OF IDIOTYPIC VACCINES.
AU BRAIT M; TASSIGNON J; ISMAILI J; MARVEL J; MEEK K; LEO O; URBAIN J
CS LAB. PHYSIOL. ANIMALE, UNIV. LIBRE DE BRUXELLES, FACULTE DES SCIENCES, BRUXELLES, BELGIUM.
SO CAZENAVE, P.-A. (ED.). PROGRESS IN VACCINOLOGY, VOL. 3. ANTI-IDIOTYPIC VACCINES. XII+139P. SPRINGER-VERLAG NEW YORK, INC.: SECAUCUS, NEW JERSEY, USA; BERLIN, GERMANY. ILLUS. 0 (0). 1991. 1-7. CODEN: PRVAEL ISBN: 0-387-97142-4; 3-540-97142-4
LA English

L10 ANSWER 21 OF 23 CAPLUS COPYRIGHT 1998 ACS
AN 1994:6769 CAPLUS
DN 120:6769
TI Method for in vitro proliferation of **dendritic** cell precursors and their use to produce immunogen
IN Steinman, Ralph M.; Inaba, Kayo; Schuler, Gerold
PA USA
SO PCT Int. Appl., 126 pp.
CODEN: PIXXD2
PI WO 9320185 A1 931014
DS W: AU, CA, FI, JP
RW: AT, BE, CH, DE, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 93-US3141 930401
PRAI US 92-861612 920401
US 92-981357 921125
DT Patent
LA English
AB A cell population enriched in **dendritic** leukocyte precursors is produced from a tissue source (e.g. blood, bone marrow) contg. the precursor cells by (1) treating the tissue with antibodies specific for antigens not present on **dendritic** precursor cells (e.g. Ia antigen, T-cell antigens, mature **dendritic** cell antigens) to kill extraneous cells, or otherwise sepg. extraneous cells; (2) culturing the tissue on a substrate in an medium contg. GM-CSF to obtain nonadherent cells and cell clusters; (3) subculturing the latter to produce cell aggregates comprising proliferating **dendritic** cell precursors; (4) serially subculturing the cell aggregates .gtoreq.1 time to enrich the proportion of **dendritic** cell precursors. Mature **dendritic** cells produced by further culture of the precursors are pulsed with an antigen and allowed to process the antigen; the resulting modified antigen, or the cells expressing it, may be used as a vaccine for treatment of autoimmune or **infectious diseases**. Thus, mouse blood leukocytes were cultured in RPMI 1640 medium contg. 5% fetal calf serum and GM-CSF (30 U/mL), and the nonadherent cell aggregates were sepd. from adherent cells. **Dendritic** cell precursors from these aggregates showed strong accessory activity in the mixed lymphocyte response and, when injected peripherally, homed to the T areas of the draining lymph nodes.

L10 ANSWER 22 OF 23 CAPLUS COPYRIGHT 1998 ACS
AN 1993:37218 CAPLUS
DN 118:37218
TI Synthetic peptide vaccine engineering: design and synthesis of

unambiguous peptide-based vaccines containing multiple peptide antigens for malaria and hepatitis
AU Tam, James P.; Lu, Yi An
CS Rockefeller Univ., New York, NY, 10021, USA
SO Innovation Perspect. Solid Phase Synth. Collect. Pap., Int. Symp., 1st (1990), Meeting Date 1989, 351-70. Editor(s): Epton, Roger. Publisher: SPCC (UK), Birmingham, UK.
CODEN: 58IYAT
DT Conference
LA English
AB Chem. defined models, known as the multiple antigen peptide (MAP) system are being designed to engineer specifically for synthetic peptide vaccines. MAPs are comprised of an oligomeric branching lysine as the core and multiple copies of peptide antigens as **dendritic** branches. Different peptide antigens such as B and T helper epitopes could be incorporated and amplified in a specific and deliberate manner. Three general designs of these chem. unambiguous MAP models were tested in two **infectious disease** systems: malaria and hepatitis. High titers of antibodies that recognized both native proteins from which they were derived were elicited by immunization with MAPs. Furthermore, in the malaria model, the level of serum antibodies correlated with protection from malaria infection, and significant protection against challenge with 2000 sporozoites was obsd. in mice immunized with MAPs. Thus, a synthetic, multiple-epitope, peptide-based immunogen with a chem. unambiguous structure may be a suitable candidate for the development of vaccines against **infectious diseases**.

L10 ANSWER 23 OF 23 WPIDS COPYRIGHT 1998 DERWENT INFORMATION LTD
AN 94-048532 [06] WPIDS
DNN N94-038216 DNC C94-021909
TI Activating T cells by using **dendritic** cells for antigen presentation - in vivo or in vitro to prime or neprime immune response, e.g. for treating or preventing infections, e.g. HIV, or cancer, also sepn. of **dendritic** cells by density gradient centrifugation.
DC B04 D16 S03
IN ENGLEMAN, E G; MARKOWICZ, S; MEHTA, A
PA (STRD) UNIV LELAND STANFORD JUNIOR
CYC 22
PI WO 9402156 A1 940203 (9406)* 48 pp
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA FI JP NO NZ
AU 9346789 A 940214 (9425)
ADT WO 9402156 A1 WO 93-US6653 930715; AU 9346789 A AU 93-46789 930715, WO 93-US6653 930715
FDT AU 9346789 A Based on WO 9402156
PRAI US 92-915972 920716
AB WO 9402156 A UPAB: 940613
Activated, antigen (Ag)-specific human T-cells are prepd. in vitro by co-culturing T cells, with isolated human **dendritic** cells (DC) exposed to Ag, so that the T cells,. are activated to proliferate or to become cytotoxic in response to Ag.
Also new are (1) similar in vivo activation process by admin. of Ag-exposed DC; (2) identification of Ag recognition by T cells by incutabing there cells with Ag-exposed DC then measuring proliferation, cytotoxicity or lymphokine prodn., and (3) isolation of DC from a mixed population of sequental density gradient centrifugation in absence of xenogenic protein to give a final population contg. at least 30% DC. Pref. the T cells are CDA or CD8 positive and Ag is a whole organism (specifically a whole virus), (poly) peptide or tumour cell.
USE/ADVANTAGE - The activated T cells can be used adoptive cellular immunotherapy agent **infectious diseases**

or cancer. DC are more effective as antigen-preventing cells than monocytes, for bother complex protein and small peptide antigens.

In an example, high purity DC were cultured with autologous CD4 positive T cells in presence of kehole limpet haemocyanin (KLH) or sperm whale myoglobin (SWM) and proliferatin measured by 3H-thymidine incoporation. The fig. shows that with both antigens a prim. T cell response was induced. Monocytes treated the same way did not generate a response. Division of the T cells into naive (UCHL-1 negative) and memory (UCHL-1 positive) subsets and repeption of the test indicated that the response was predominantly from naive cells.

Dwg.5A/9

(FILE 'HOME' ENTERED AT 16:35:21 ON 03 FEB 1998)

FILE 'MEDLINE' ENTERED AT 16:35:51 ON 03 FEB 1998

L1	120	S	FLT3 LIGAND
L2	23	S	L1 NOT PY>1995
L3	38	S	(L1 OR FL) AND DENDRITIC
L4	0	S	L2 AND L3
L5	10410	S	INFECTIOUS DISEASE#
L6	24	S	L5 AND DENDRITIC

FILE 'MEDLINE, BIOSIS, CAPLUS, WPIDS' ENTERED AT 17:04:19 ON 03 FEB 1998

L7	175	S	L3 OR L6
L8	103		DUPLICATE REMOVE L7 (72 DUPLICATES REMOVED)
L9	44	S	L8 NOT PY>1995
L10	23	S	L9 NOT L3
L11	21	S	L9 NOT L6